SYNTHESES AND APPLICATIONS OF 5-BENZOTRIAZOLE PYRROLIDINONES AND 3-BENZOTRIAZOLE ISOINDOLINONES

By

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To my Parents

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TABLE OF CONTENTS

page

ACKNOWLEDGMENTS iii

ABSTRACT vii

CHAPTERS

1 INTRODUCTION 1

1.1 General Introduction 1

1.2 Benzotriazole Chemistry 1

2 PREPARATION OF 1,5-DISUBSTITUTED PYRROLIDIN-2-ONES 11

2.1 Introduction 11

2.2 Results and Discussion 14

2.3 Experimental Section 24

3 SYNTHESES OF PYRROLO- AND INDOLO-ISOQUINOLINONES BY INTRAMOLECULAR CYCLIZATIONS OF 1-ARYLETHYL-5-BENZOTRIAZOLYL-PYRROLIDIN-2-ONES AND 3-BENZOTRIAZOLYL-2-ARYLETHYL-1-ISOINDOLINONES 43

3.1 Introduction 43

3.2 Results and Discussion 46

3.3 Experimental Section. 54

4 SYNTHESES OF BENZODIAZEPINES, BENZOXAZEPINES AND BENZOTHIAZEPINES BY CYCLIZATIONS OF 1-HETEROARYLPROPYL-5-BENZOTRIAZOLYL-PYRROLIDIN-2-ONES AND 3-BENZOTRIAZOLYL-2-HETEROARYLPROPYL-1-ISOINDOLINONES 60

4.1 Introduction 60

4.2 Results and Discussion 63

4.3 Experimental Section 72

5 SYNTHESES OF HETEROARYL BENZOTRIAZOLES BY MANNICH CONDENSATIONS 79

5.1 Introduction 79

5.2 Results and Discussion 84

5.3 Experimental Section 91

6 SUMMARY AND CONCLUSIONS 101

LIST OF REFERENCES 111

BIOGRAPHICAL SKETCH 120

Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
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SYNTHESES AND APPLICATIONS OF 5-BENZOTRIAZOLE PYRROLIDINONES AND 3-BENZOTRIAZOLE ISOINDOLINONES

By

Shamal Mehta

December 2000

Chairman: Dr. Alan R. Katritzky
Major Department: Chemistry

Benzotriazole has been shown to be a versatile molecule in organic synthesis. It is used as an inexpensive, stable and highly useful synthetic auxiliary. The synthesis and utility of several types of benzotriazole containing intermediates have been explored.

We have developed a synthesis of 5-benzotriazole substituted pyrrolidin-2-ones from 2,5-dimethoxy-2,5-dihydrofuran, primary amines and benzotriazole. We were able to show that by the replacement of the benzotriazole group with silane reagents, zinc regents and phosphorus reagents, 1,5-disubstituted pyrrolidine-2-ones could be prepared.

We have developed a synthesis of pyrrolo-isoquinolinones and indolo-isoquinolinones by intramolecular cyclizations of 1-arylethyl-5-benzotriazolyl-pyrrolidin-2-ones and 3-benzotriazolyl-2-arylethyl-1-isoindolinones. Thus, 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones were prepared by intramolecular cyclizations of 1-arylethyl-5-benzotriazolyl-pyrrolidin-2-ones and 3-benzotriazolyl-2-arylethyl-1-isoindolinones

respectively, in the presence of titanium chloride. High stereoselectivity was observed in products prepared from chiral amines.

In addition we have developed a method for the synthesis of chiral benzodiazepines, benzoxapines and benzthiazopines. Lewis acid mediated cyclizations of readily available starting materials produced novel benzodiazepines, benzoxazepines and benzothiazepines in high yields. The advantage of this method is that these compounds can be made in only a few steps from readily available starting materials.

We have also described the synthesis of heteroaryl benzotriazole compounds, *N*-substituted-2-(benzotriazol-1-yl)isoindoles and pyrroles, and 2-(benzotriazol-1-yl)furan. Efficient one step syntheses of *N*-substituted-2-(benzotriazol-1-yl) isoindoles and pyrroles were effected by reactions of primary amines with *o*-phthalaldehyde or 2,5-dimethoxy-2,5-dihydrofuran respectively in the presence of benzotriazole. Reaction of 2,5-dimethoxy-2,5-dihydrofuran with benzotriazole gave 2-(benzotriazol-1-yl)furan.

Thus, by incorporating the benzotriazole moiety into molecules during a synthetic sequence, we were able to obtain new compounds efficiently in good yields, showing the versatility of benzotriazole as a synthetic auxiliary

CHAPTER 1
INTRODUCTION

1.1 General Introduction

In 1828, Fredrich Wohler, a German scientist, synthesized urea by heating ammonium cyanate. This was the first synthesis of an organic molecule. For the past 150 years chemists have been interested in synthesizing compounds that could be commercially useful, used as dyes, drugs and industrial chemicals. Some of the defining molecules occurring in nature that have been synthesized during the last 50 years have been Penicillin (Sheehan), Chlorophyll and Quinine (Woodward), and DNA (Khorana). A majority of these molecules and others contain heterocyclic units. Thus methods for 'atom economy' in the synthesis of heterocycles are very important.

1.2 Benzotriazole Chemistry

Benzotriazole (BtH) (**1.1**) (Figure 1.1) has been shown to be a very useful molecule in organic synthesis [98CRV409]. It is used as an inexpensive, stable and highly useful synthetic auxiliary as it possesses the following properties:

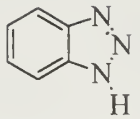
A. It is easily introduced into a molecule at the beginning of a synthetic sequence. Thus it has found wide applicability in the synthesis of biologically active heterocyclic molecules. There are a number of methods to introduce benzotriazole into a molecule and will be discussed later in this chapter.

B. It is stable to a variety of organic manipulations. It is stable to thermal conditions (400°C), hot concentrated H_2SO_4, KOH, oxidizers ($KMnO_4$) and strong reducing agents such as $LiAlH_4$ and H_2-Pd.

C. It has a strong acidity (pKa = 8.2) which endows it with useful properties *viz.* it activates a portion of the molecule to further transformations. It is a Lewis base of appreciable strength but a very weak Bronsted base (pKa < 0 for the addition of a proton).

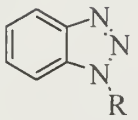
D. It is easily removed at the end of a synthetic sequence. This removal is relatively straightforward. It normally involves either displacement with a nucleophile, hydrolysis or a simple organic manipulation. It does not require polluting heavy metals or strong oxidizing agents.

Thus the Bt group has often been compared to a halogen substituent. However, Bt-containing compounds are much less active and more stable than their halogen analogues, which are sometimes physiologically dangerous. While a number of transformations, such as anion formation by abstraction of the α-hydrogen, can be performed on substituted benzotriazoles, these cannot be carried out on halogen containing compounds.



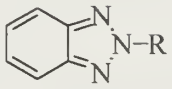
Benzotriazole (BtH)

1.1



Bt^1-R

1.2a



Bt^2-R

1.2b

Figure 1.1

N-substituted benzotriazoles (Bt-R) exist as the benzotriazol-1-yl (Bt^1) (**1.2a)** and the benzotriazol-2-yl (Bt^2) (**1.2b**) isomers (Figure 1.1). Though these two isomers have different R_f values, they *have the same order of stability and show similar reactivity.* In addition, depending on the functionalities present adjacent to the Bt group, these isomers have been shown to interconvert in solution (Figure 1.2) via intermediate **1.5**.

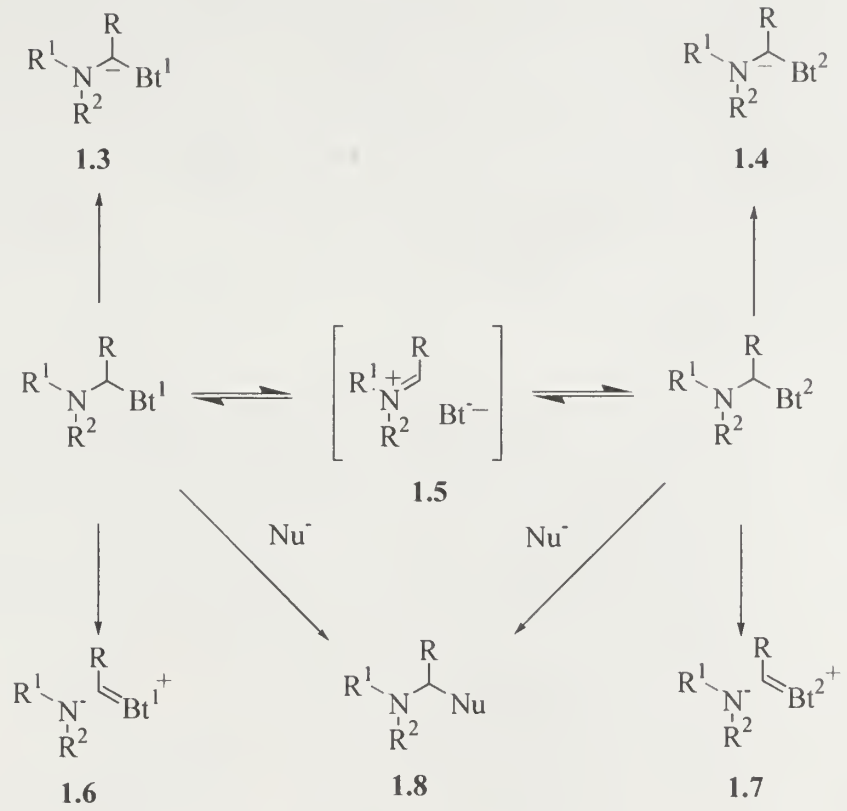


Figure 1.2

Benzotriazole exhibits several important properties when attached to a molecule. It can activate the α-hydrogen of compound **1.9** to a proton loss to form the Bt carbanion **1.10** (Figure 1.3) due to the negative inductive effect of the three electron withdrawing nitrogen atoms. Furthermore, when there is a α-heteroatom present in the molecule, it can facilitate ionization by cleavage of either (a) the Bt-C bond (for amino, alkoxy or thioalkoxy groups) to give **1.13** or (b) the heteroatom-C bond (for halogen or hydroxyl groups) to give the iminium ion **1.15**. The resulting carbocation is stabilized by the lone pair of electrons on the nitrogen atom at the 1-position. This holds true even if the

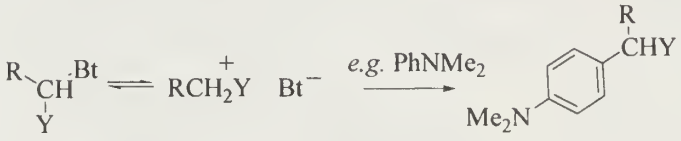
nitrogen is replaced by a sulfur or oxygen atom. Finally, it is a good leaving group and hence can easily be displaced by nucleophiles to give **1.19**. In addition it could also leave when activated by electron donating groups (*e.g.* α-heteroatoms, heterocycles, aryl or alkenyl groups).

A. Bt as an proton activator

1.9 **1.10** **1.11**

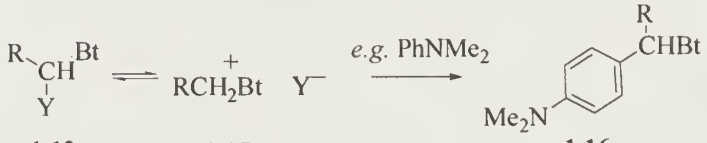
B. Bt as a cation stabilizer

(a): Cleavage of the Bt - C bond.



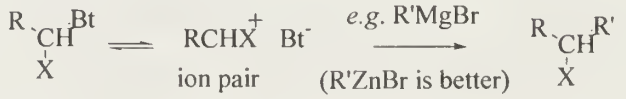
1.12 **1.13** **1.14**

(b): Cleavage of the Y - C bond.



1.12 **1.15** **1.16**

C. Bt as a leaving group



1.17 **1.18** **1.19**

Figure 1.3

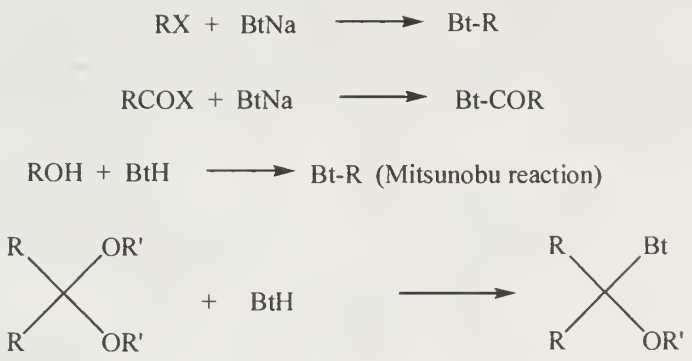
For the past decade and half, the Katritzky group has been actively researching and developing new methodologies for benzotriazole application in chemical syntheses. The work of this thesis is an effort to further our understanding of benzotriazole chemistry and increase its utility in organic synthesis.

1.2.1 Introduction of Benzotriazolyl Groups into a Molecule

It is extremely easy to introduce benzotriazole into a complex organic molecule. There are a number of methods to introduce benzotriazole into compounds. They are three important methods.

The first is the nucleophilic substitution of a halide, hydroxide or an alkoxide moiety to produce a Bt-C bond: For the nucleophilic displacement of halogens by Bt numerous methods are available [94S597, 96JHC2031, 95H13, 94H793]. The displacement of a hydroxyl group, such as that of formic acid, has also been accomplished in the presence of di-cyclohexyl urea [95S503]. Unactivated alcohols cannot be directly converted to alkyl benzotriazoles. They have to be converted to the sodium alkoxides and be treated with 1,1,-sulfonyldibenzotriazole to give, *via* an unstable intermediate, a mixture of the Bt^1 and Bt^2 isomers [93H1253]. Dialkyl acetals, and orthoformates readily react with Bt to displace one of the alkoxy groups [89JOC6022, 91S279]. Reaction of Bt with acid halides can also be accomplished. Finally treatment of an acetal with benzotriazole causes replacement of one of the acetals with Bt (Figure 1.4).

A. NUCLEOPHILIC SUBSTITUTION



B. ADDITION

Addition to C-heteroatom multiple bonds C=O, C=N, C=N+, C=S

Addition to to electron deficient C-C multiple bonds by Michael addition

Addition to electron-rich C-C multiple bonds (enol ethers, enamines, enamides, vinyl sulfides)

Figure 1.4

The second method involves the addition of BtH to *pi* bonds: BtH can easily add to enones, amides and electron rich olefins such as enamines, enamides or vinyl ethers [92S1295] (Figure 1.4).

Finally, reaction of a carbonyl compound, Bt and an amine, under mild acid catalysis or dehydrating conditions gives the N-(α-aminoalkyl)benzotriazoles [90CB1443]. This is a three component or double addition reaction. In this case, the X group could be oxygen, nitrogen or sulfur.

1.2.2 Substitution of Benzotriazole Groups from a Molecule

There are numerous methods to remove benzotriazole from a molecule. In this thesis three methods have been used. The first is the addition of pi bonds of enamides or enones to immonium benzotriazolides. 1-(α-Aminoalkyl)benzotriazole exist in solution in equilibrium with ion pair **1.5** which is the intermediate for the interconversion of the benzotriazol-1-yl and benzotriazol-2-yl isomers (Figure 1.2). Enamines, enamides and electron rich double bonds can all add to these ion pairs. Examples of these substitutions are shown both in Chapter 2 as well as in Chapter 3.

The second method is the addition of pi bonds or lone pairs to oxonium or thiazonium benzotriazolides. 1-(α-Alkoxyalkyl)benzotriazoles also exist in solution in equilibrium the with benzotriazolyl anion and carboxonium cation pairs. However due to the lesser stabilizing effect of an alkoxy group as compared to that of an amino group, additional stability of an aromatic group is sometimes required. However, we have shown (Chapter 4) that for an intermolecular cyclization no such additional stabilization is required. The same argument holds true for thiazonium benzotriazoles.

The last method involves the removal of Bt by nucleophilic substitution. Grignard reagents, organozinc reagents, organolithium reagents and hydrides can easily displace Benzotriazole in systems having a Bt-C-N unit. The displacement of benzotriazole from 5-benzotriazole pyrrolidin-2-ones has been demonstrated in chapter 2.

1.2.3 Reactions of 5-benzotriazole pyrrolidin-2-ones and 3-benzotriazole isoindolones

There are three interesting methods of functionalizing 5-benzotriazole pyrrolidin-2-ones and 3-benzotriazole isoindolones. One of them is via the formation of radicals. Treatment of 1-(α-aminoalkyl)benzotriazole with Li metal or a radical initiator produces a radical at the 5-position of the pyrrolidin-2-ones. This radical could be trapped to give 5-substituted pyrrolidin-2-ones. Another method is the formation of an anion at the 5-position of the pyrrolidin-2-ones. Reaction of 5-benzotriazole pyrrolidin-2-ones with excess base produces the anion at the 5-position and this could be treated with a suitable electrophile to put in a single substituent at the 5-position. This would give us 5-substituted 5-benzotriazole pyrrolidin-2-ones. Alternatively, the benzotriazole group could be displaced from 5-substituted 5-benzotriazole pyrrolidin-2-ones to synthesize 5,5-disubstituted pyrrolidin-2-ones. The last method is via the formation of imminium ions. In the presence of Lewis acids, elimination of benzotriazole from the 5-benzotriazole pyrrolidin-2-ones and 3-benzotriazole isoindolones produced iminium ions, which could be reacted with suitable nucleophiles, *pi* bonds or aryl groups (Figure 1.3).

To date, a lot of work has been done in our group on the radical and anionic reactions of 1-(α-aminoalkyl)benzotriazole containing molecules [98CRV409]. This

thesis is primarily concerned with the synthesis of 5-benzotriazole pyrrolidin-2-ones and 3-benzotriazole isoindolones, and their transformations to biologically important compounds. These substrates were further utilized for the synthesis of a variety of fused and cyclic heterocyclic systems.

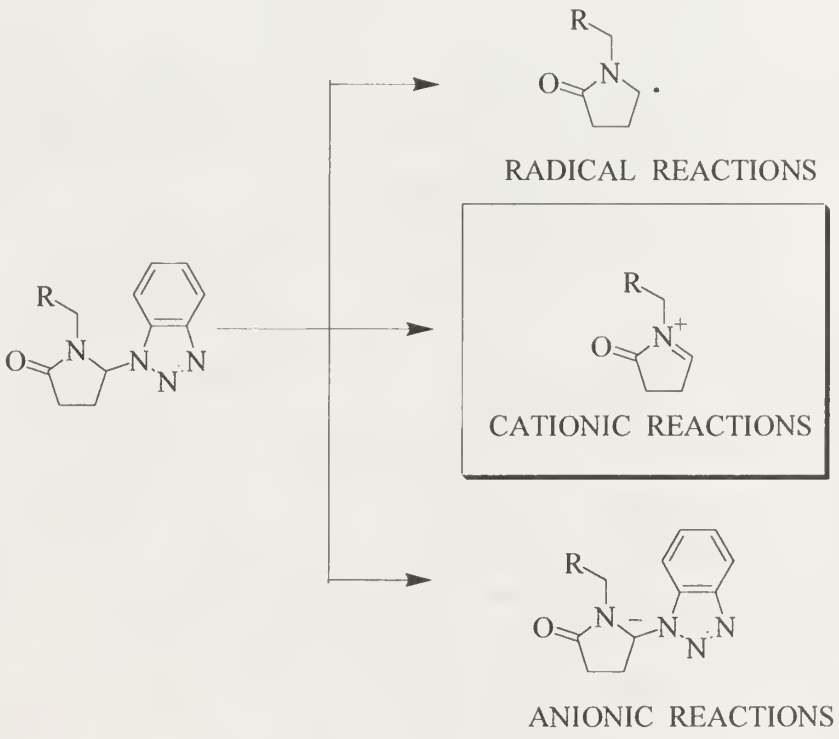


Figure 1.5

CHAPTER 2
PREPARATION OF 1,5-DISUBSTITUTED PYRROLIDIN-2-ONES

2.1 Introduction

Pyrrolidin-2-ones possess varied biological activity and have been used extensively as pharmaceuticals [95COS209, 94JMC3542, 95JMC1593, 95S772]. Consequently there is an ongoing interest in the synthesis of substituted pyrrolidin-2-ones. They are also excellent intermediates for the synthesis of pyrrolidine alkaloids and γ-amino acids [84JA1877, 84TL3115, 98T12547, 93JOC4010, 93S295]. Although the preparation of pyrrolidin-2-ones has been much studied [91JOC4868, 98JA7429, 92JOC1656, 97TA2001, 96TA2365, 98T12547, 91JA9858, 91TL401], there is still considerable interest in exploring newer synthetic routes. We now report a novel synthesis of 1,5-disubstituted pyrrolidin-2-ones via the benzotriazole methodology [98CR409].

Typical routes to 1,5-disubstituted pyrrolidin-2-ones can be classified as follows (Figure 2.1):

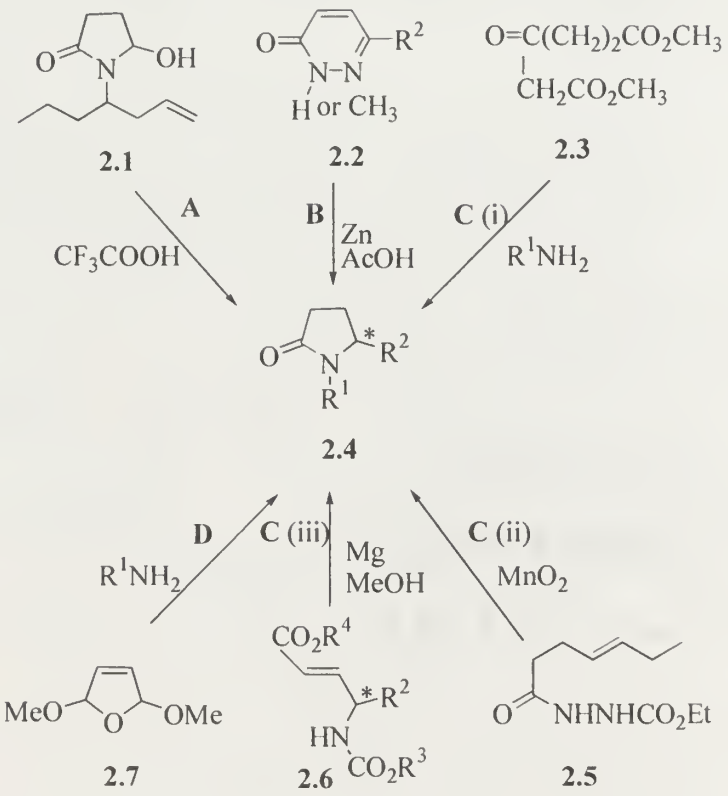


Figure 2.1

A. Treatment of carbinolamide (**2.1**) with CF_3COOH gave a ring-closure product **2.4** [R^1, R^2 = -$CH(CH_2CH_2CH_3)CH_2CH(O_2CCF_3)CH_2$-] [81TL1567]:

B. Reductive ring-contraction of pyridazin-3-ones (**2.2**) by Zn in AcOH formed **2.4** (R^1 = H or CH_3, R^2 = aryl) [84JCS(CC)1373].

C. Ring-closure reactions of

A. (i) Dimethyl 3-oxohexanedioate (**2.3**) with primary amines to **2.4** (R^1 = H or alkyl, $R^2 = CH_2CO_2CH_3$) [88JHC1275],

B. (ii) γ,δ-Unsaturated hydrazide (**2.5**) with active MnO_2 to **2.4** ($R^1 = NHCO_2Et$, $R^2 = CH{=}CHCH_3$) [79TL4185] and

C. (iii) γ-Amino-α,β-unsaturated carboxylate (**2.6**) with magnesium in methanol to **2.4** (R^1 = H, R^2 = alkyl) [93TL4439].

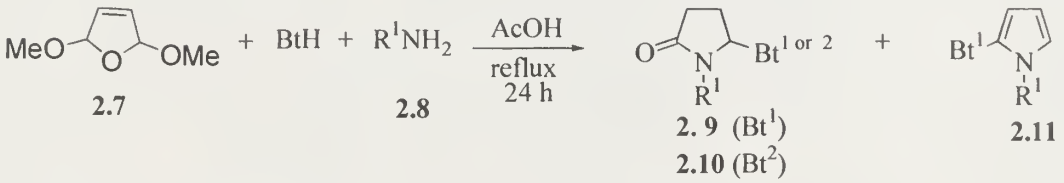
D. Reaction of 2,5-dimethoxy-2,5-dihydrofuran (**2.7**) and primary amines in refluxing acetic acid produced **2.4** (R^2 = alkoxy) [94TL3931, 98T10403].

The methods as reported above generally introduce the R^2 (alkyl or aryl) group into the pyrrolidin-2-one ring directly from the starting material, rather than its introduction after the formation of the 5-membered pyrrolidin-2-one ring. Because of the strong C-C bond between R^2 and the ring, it is difficult subsequently to replace such R^2 groups by other functional groups. However, if R^2 were a benzotriazole moiety, the much weaker C-N bond of the *N*-substituted benzotriazoles should allow easy removal and replacement of the Bt group by other groups via nucleophilic substitution, elimination, reduction and cyclization [98CR409]. We report herein the synthesis of 5-benzotriazolyl-1-substituted-pyrrolidin-2-ones as versatile synthons and their novel reactions with allylsilanes, organozinc reagents and phosphorus compounds to generate 1,5-disubstituted pyrrolidin-2-ones.

2.2 Results and Discussion

2.2.1 Preparation of 5-Benzotriazolyl-1-Substituted-Pyrrolidin-2-ones (**2.9**) and (**2.10**)

The reaction of 2,5-dimethoxy-2,5-dihydrofuran (**2.7**), benzotriazole and primary amine **2.8** in refluxing AcOH for 24 h gave 5-(benzotriazol-1-yl)-1-substituted-pyrrolidin-2-one (**2.9**) and 5-(benzotriazol-2-yl)-1-substituted-pyrrolidin-2-one (**2.10**), along with a minor by-product 1-(1-substituted-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**2.11**) (Figure 2.2).



2.7 **2.8** **2. 9** (Bt^1) **2.10** (Bt^2) **2.11**

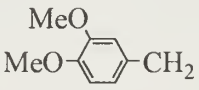
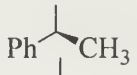
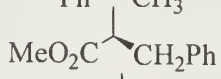
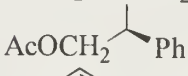
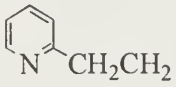
$Bt^{1\text{ or }2}$ = benzotriazol-1-(or -2)-yl

Figure 2.2

Bt^1 isomer **2.9** and Bt^2 isomer **2.10** were separated by column chromatography (silica gel), with the Bt^1 isomer as the major constituent. Although some of the intermediates, e.g., **2.9a**, **2.9c**, **2.9f**, **2.9g**, **2.9i-k**, **2.10b**, and **2.10f-k**, were not fully characterized possibly due to easy oxidation, they had clear ^1H and ^{13}C NMR spectra and their nucleophilic reactions with allylsilanes, organozinc reagents and phosphorus compounds also afforded fully characterized 1,5-disubstituted pyrrolidin-2-ones as

expected. The combined yields of **2.9** and **2.10** are from good to excellent (Table 2.1). Methyl (2*S*)-2-amino-3-phenylpropanoate gave the expected intermediate (**2.9i**), which shows that commercially available chiral amino acid esters could be used for the

Table 2.1 Isolated yields of **2.9**, **2.10** and **2.11**

No.	R^1	2.9	2.10	2.11
a	Ph	70	[a]	10
b	$PhCH_2$	69	10	5
c	$PhCH_2CH_2$	66	14	1
d	*p*-$MeOC_6H_4CH_2$	64	14	[a]
e	*p*-$MeOC_6H_4CH_2CH_2$	63	9	[a]
f [b]	$CH_3COOCH_2CH_2$	65 [d]	16 [d]	[a]
g		74	9	[a]
h		67	15	2
i		66	18	[a]
j [c]		60	13	5
k		66	14	[a]

[a] No detectable amount of the product was isolated.
[b] $HOCH_2CH_2NH_2$ was used, but **2.9f** and **2.10f** were obtained as esters due to the presence of CH_3COOH.
[c] (*S*)-$PhCH(CH_2OH)NH_2$ was used, but **2.9j**, **2.10j** and **2.11j** were obtained as esters due to the presence of CH_3COOH.
[d] Yields estimated by ^1H NMR spectrum.

preparation of 1,5-disubstituted pyrrolidin-2-ones, although the expected product could not be isolated when (2*S*)-2-amino-3-phenylpropanoic acid was used. With chiral primary

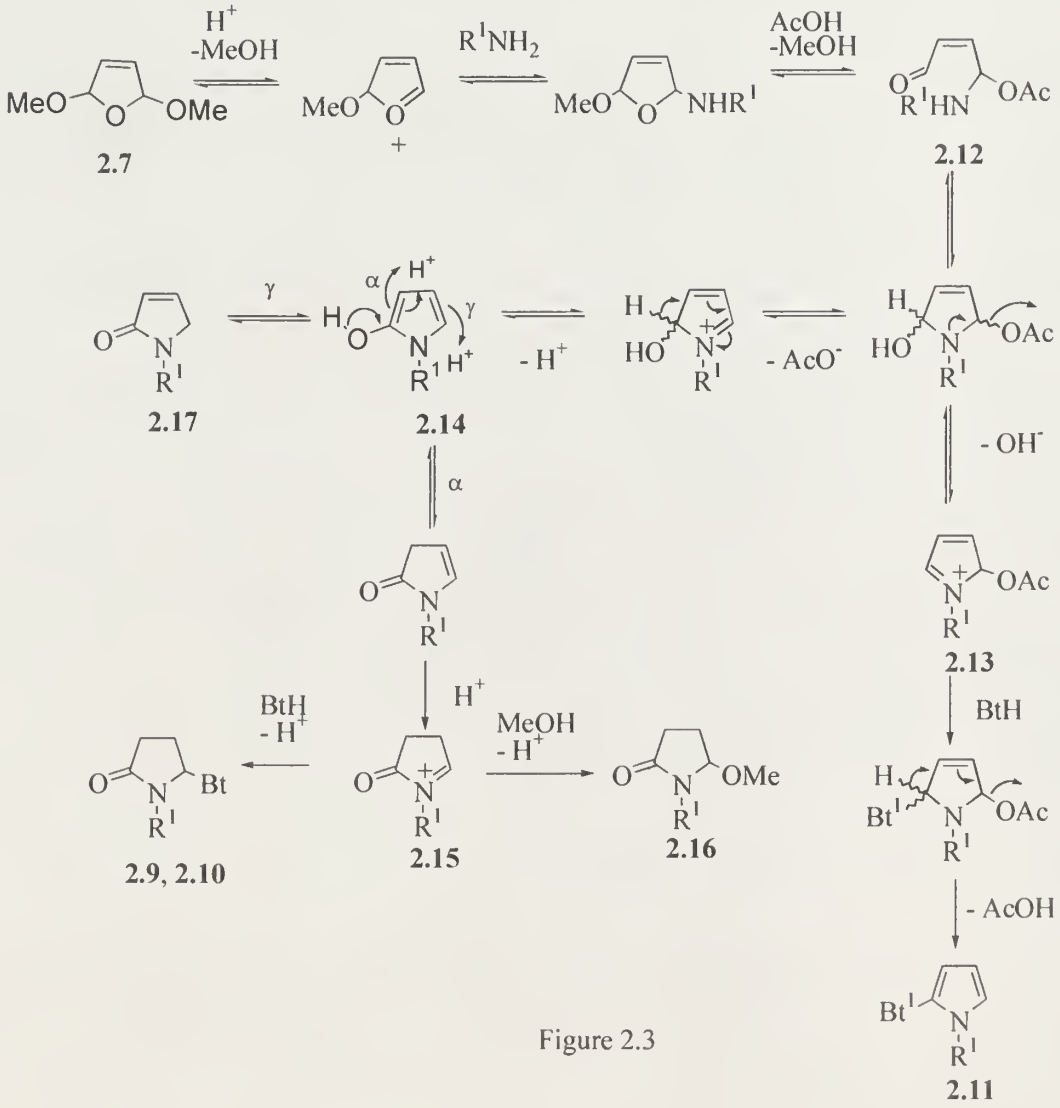


Figure 2.3

amines, the intermediates **2.9h–j** and **2.10h–j** were obtained, but there was little chiral control at the 5-position, as seen from the ^{1}H and ^{13}C NMR spectra. We were unable to isolate either the two Bt^1 diastereomers or the two Bt^2 diastereomers.

The proposed mechanism for the reaction of **2.7** and R^1NH_2 involves a competitive α- and γ-tautomerization of the 2-hydroxypyrrole (**2.14**), leading to the formation of 5-methoxypyrrolidin-2-one (**2.16**) and the conjugated pyrrolinone (**2.17**), respectively (Figure 2.3) [98T10403]. Compound **2.16** is formed *via* the transient iminium cation **2.15**.

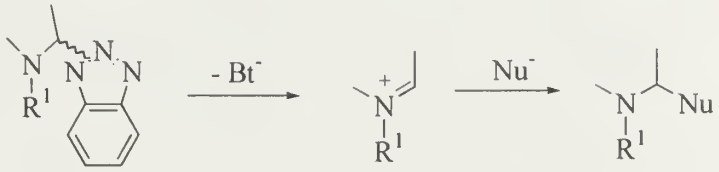
We believe that in our reaction, 2-hydroxypyrrole (**2.14**) forms the same transient iminium cation **2.15**, which immediately reacts with BtH to produce 5-benzotriazolyl-1-substituted-pyrrolidin-2-ones (**2.9**) and (**2.10**) [89JCS(P1)225, 94S907]. The conjugated pyrrolinone (**2.17**) was not detected in our reaction. In addition, the intramolecular condensation of the formyl group and the secondary amine in the intermediate **2.12** generates the transient iminium cation **2.13**, which reacts with BtH, with the subsequent elimination of AcOH to afford the minor product α-(benzotriazol-1-yl)pyrrole (**2.11**).

Our previous work [90JOC3205, 91T2683, 98JOC6699] has demonstrated that

A. Bt^1 and Bt^2 groups are both good leaving groups and can be replaced by a nucleophile;

B. The mechanism of nucleophilic substitution of the Bt group by the adduct X involves a planar iminium salt Y as intermediate (Figure 2.4).

Therefore, the position at which the substituent is attached to the benzotriazole ring is not important. Thus, the mixture of intermediates **2.9** and **2.10** could be used for the subsequent nucleophilic substitutions with allylsilanes, organozinc reagents and phosphorus compounds.



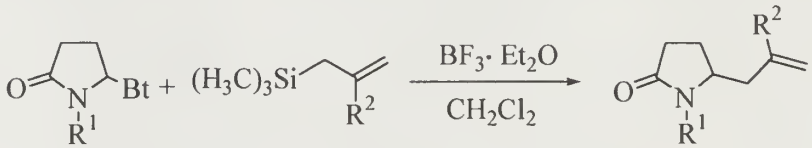
X **Y** **Z**

Figure 2.4

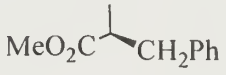
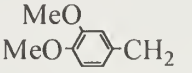
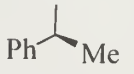
2.2.2 Substitution of the Benzotriazole Group from **2.9** using Allylsilanes

Initially, it was necessary to confirm that there was no difference in the reactivity of the Bt^1 isomer **2.9** and the Bt^2 isomer **2.10**. Hence, **2.9b** (R^1 = $PhCH_2$), **2.9c** (R^1 = $PhCH_2CH_2$), **2.10b** (R^1 = $PhCH_2$), and **2.10c** (R^1 = $PhCH_2CH_2$) were each separately reacted with allyl(trimethyl)silane in the presence of $BF_3 \cdot Et_2O$. The yields of **2.18a**, generated from **2.9b** and **2.10b** were 90% and 87% respectively; and the yields of **2.18b**, generated from **2.9c** and **2.10c** were 90% and 90% respectively (Figure 2.5). These results prove that both the Bt^1 isomer and Bt^2 isomer have no significant difference in their reactivities and lead to the same products in very similar yields. In order to compare and

discuss the results of different reactions with varying substituents, the same experiments were carried out by using only the pure Bt^1 isomer **2.9** as the starting material.



2.9 **2.18a-g**

2.18	R^1	R^2	Yield (%)
a	$PhCH_2$	H	90 (87)[a]
b	$PhCH_2CH_2$	H	90 (90)[a]
c	$PhCH_2CH_2$	CH_3	84
d	*p*-$MeOC_6H_4CH_2$	CH_3	80
e	*p*-$MeOC_6H_4CH_2CH_2$	H	85
f	*p*-$MeOC_6H_4CH_2CH_2$	CH_3	80
g		H	49
h		H	*b*
i		H	*b*

[a] The yield in brackets was obtained from Bt^2 isomer **2.10**.

[b] No desired product was isolated.

Figure 2.5

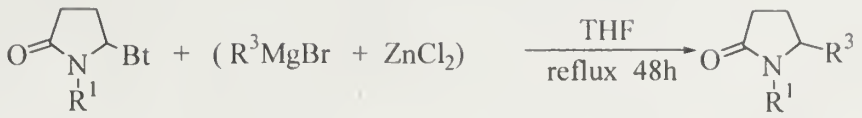
Treatment of intermediates **2.9b–e** and **2.9i** with 4 equiv of trimethylallyl- or trimethyl(2-methylallyl)-silane in the presence of $BF_3 \cdot Et_2O$ at 0°C furnished 1-substituted-5-allylpyrrolidin-2-ones (**2.18a–f**) in 80–90% yield and **2.18g** in 49% yield (Figure 2.5). The structures of **2.18a–g** were confirmed by the ^1H, ^{13}C NMR spectra and high-resolution mass spectra (HRMS). The Bt group of **2.9** serves as a good leaving group and is easily eliminated in the presence of $BF_3 \cdot Et_2O$ to generate iminium cation **Y**, which is subsequently attacked by the nucleophile allylsilane to afford the 1-substituted-5-allylpyrrolidin-2-ones (**2.18a–g**). Thus, by using benzotriazole methodology, an allyl group is easily introduced into the 5-position of the pyrrolidin-2-one ring. However, **2.18g** was obtained as diastereoisomers, which meant that the *N*-(chiral)substituted group could not influence the reactivity at the 5-position chiral center.

It is interesting to note that compounds **2.18h** and **2.18i** did not provide us with any 5-substituted product. Compound **2.18h** has two vicinal oxygens on the aromatic ring which could σ-bond with the Lewis acid. Thus Lewis acid would no longer be activated enough to rip out the benzotriazole to form the reactive imminium ion (which would then react with the silane reagent). Compound **2.18i** having a chiral substituent α to the nitrogen did not react with the Lewis acid and the silane reagent. This may be due to the fact that on formation of the imminium ion, attack by the incoming nucleophile should be perpendicular to the plane of the imminium ion. We believe that unfavourable steric congestion near the site of reaction causes the improper orientation of the Lewis acid and

the incoming silane reagent. Thus the reaction does not occur.

2.2.3 Substitution of the Benzotriazole Group from **2.9** using Organozinc Reagents

Grignard reagents cannot be directly used for the nucleophilic substitution of **2.9**, since they react with the cyclic amide group. Treatment of **2.9b** and **2.9e** with 3 equiv of organozinc reagent, generated by the reaction of the Grignard reagents and zinc chloride, in THF at reflux gave 1,5-disubstituted pyrrolidin-2-ones (**2.19a–g**) in moderate to excellent yields; while treatment of **2.9e** with 3 equiv of 2-bromomalonate and zinc powder in refluxing THF afforded **2.19h** in 67% yield (Figure 2.6). The structures of **2.19a–h** were determined by the ^{1}H, ^{13}C NMR as well as HRMS. The nucleophilic substitution of **2.9** with organozinc reagents thus allows the introduction of various substituents, e.g., propynyl, vinyl, propenyl, benzyl, cyclopentyl, pentyl and ester, into the 5-position of the pyrrolidin-2-one rings.



2.9 **2.19a-h**

2.19	R^1	R^3	Yield (%)
a	$PhCH_2$	$CH_3C{\equiv}C$	49
b	*p*-$MeOC_6H_4CH_2CH_2$	$CH_3C{\equiv}C$	71
c	*p*-$MeOC_6H_4CH_2CH_2$	$CH_2{=}CH$	80
d	*p*-$MeOC_6H_4CH_2CH_2$	$CH_3CH{=}CH$	52
e	*p*-$MeOC_6H_4CH_2CH_2$	$PhCH_2$	50
f	*p*-$MeOC_6H_4CH_2CH_2$	*cyclo*-C_5H_9	57
g	*p*-$MeOC_6H_4CH_2CH_2$	*n*-C_5H_{11}	73
h[a]	*p*-$MeOC_6H_4CH_2CH_2$	$CH(COOEt)_2$	67

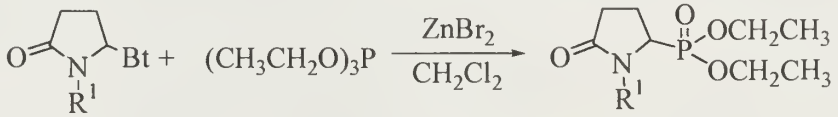
[a] Reaction condition for **2.19h**: $BrCH(COOEt)_2$, Zn

Figure 2.6

2.2.4 Substitution of the Benzotriazole Group from **2.9** by Phosphorus Nucleophiles

In 1997, Maury *et al.* reported that the cyano group of (3*R*,5*S*,8a*R*)-3-phenylhexahydro-oxazolo[3,2-*a*]pyridine-5-carbonitrile, generated from the double condensation of (*R*)-phenylglycinol and glutaraldehyde in the presence of potassium cyanide, could be replaced by a phosphono group using either triethyl- or trimethyl phosphite [97T3267]. In our reaction, treatment of **2.9d–g**, **2.9i** and **2.9j** in dry THF with triethyl phosphite in the presence of 1 equiv of $ZnBr_2$ produced diethyl 1-substituted-5-oxo-2-pyrrolidinylphosphonates **2.20a–f** in moderate to good yields (Figure 2.7). Thus

the Bt groups of **2.9d–g**, **2.9i** and **2.9j** are readily replaced with a phosphono group. The compounds **2.9f** and **2.9j** are esters and were hydrolyzed during the reaction, and thus **2.20a** and **2.20e** were obtained as primary alcohols. The structures of **2.20a–f** were determined by ^{1}H and ^{13}C NMR, and the ^{13}C NMR spectra show that phosphorus has the coupling splitting effect on some carbon peaks. Again, a chiral group at the 1-position [R^1 = (*S*)-PhCH(CH_2OH) or (*S*)-$PhCH_2CH(CO_2Me)$] did not control the chiral center at the 5-position, resulting in (**2.20e**) and (**2.20f**) being obtained as diastereoisomers.



2.9 **2.20a-f**

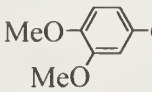
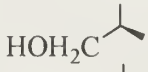
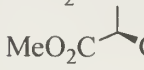
2.20	R^1	Yield (%)
a	$HOCH_2CH_2$	49
b	*p*-$MeOC_6H_4CH_2$	79
c		78
d	*p*-$MeOC_6H_4CH_2CH_2$	76
e		85
f		67

Figure 2.7

In conclusion, we have described a simple and novel route to 1,5-disubstituted pyrrolidin-2-ones via the benzotriazole methodology. Several advantages for this reaction include the following

A. The intermediates **2.9a–k** and **2.10a–k** could be obtained in one step;

B. The total yield for Bt^1 and Bt^2 isomers is from good to excellent (70% to 84%) and there is no difference in the reactivity of Bt^1 and Bt^2 isomer;

C. The compounds **2.9a–k** and **2.10a–k** are versatile synthons and can be further transformed to new 1,5-disubstituted pyrrolidin-2-ones *via* the nucleophilic substitution of the benzotriazole group with allylsilanes, organozinc reagents and phosphorus compounds.

2.3 Experimental Section

Melting points were determined on a hot-stage apparatus without correction. Column chromatography was carried out on silica gel (230-400 mesh). The ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ solution (300 MHz and 75 MHz respectively), with TMS or $CDCl_3$ as internal references.

2.3.1 General Procedure for the Preparation of 5-(Benzotriazol-1-yl)-1-Substituted-Pyrrolidin-2-Ones (**2.9**) and 5-(Benzotriazol-2-yl)-1-Substituted-Pyrrolidin-2-Ones (**2.10**)

An appropriate primary amine (25 mmol), 2,5-dimethoxy-2,5-dihydrofuran (**2.7**) (3.2 g, 25 mmol) and 1*H*-1,2,3-benzotriazole (6.5 g, 55 mmol) were dissolved in acetic acid (25 mL) and refluxed under N_2 for 24 h. After the reaction mixture was cooled, CH_2Cl_2 (50 mL) was added. The organic layer was washed with 2 M NaOH and dried over Na_2SO_4. The solvent was evaporated *in vacuo* and the residue was separated by flash chromatography (silica gel) with hexane-EtOAc (7:3) as eluent to give 5-(benzotriazol-1-yl)-1-substituted-pyrrolidin-2-ones (**2.9**) and 5-(benzotriazol-2-yl)-1-substituted-pyrrolidin-2-ones (**2.10**), together with a by-product 1-(1-substituted-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**2.11**).

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenylpyrrolidin-2-one (**2.9a**). Brown solid, mp 170–171 °C; ^{1}H NMR δ 2.57–2.63 (m, 1H), 2.80–3.00 (m, 2H), 3.13–3.22 (m, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.07–7.44 (m, 8H), 8.02 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 25.8, 30.2, 74.0, 109.0, 120.3, 124.0, 124.3, 127.0, 128.0, 129.1, 131.4, 135.8, 146.1, 173.8.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzylpyrrolidin-2-one (**2.9b**). Brown powder, m.p. 169.5–170.0 °C; ^{1}H NMR δ 2.40–2.55 (m, 1H), 2.70–2.85 (m, 2H), 3.00–3.15 (m, 1H), 3.53, 4.91 (AB, J = 15.0 Hz, 2H), 6.34 (d, J = 6.6 Hz, 1H), 7.04–7.06 (m, 2H), 7.20–7.22 (m, 4H), 7.37–7.49 (m, 2H), 8.07 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 25.2, 29.4, 44.3, 71.4, 109.0, 120.4, 124.3, 127.9, 128.0, 128.3, 128.6, 131.4, 134.8, 146.3, 174.2.

Anal. Calcd for $C_{17}H_{16}N_4O_2$: C, 69.85; H, 5.52; N, 19.16. Found: C, 69.63; H, 5.66; N, 18.93.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-phenethylpyrrolidin-2-one (**2.9c**). Brown oil; ^{1}H NMR δ 2.37–2.50 (m, 1H), 2.59–3.05 (m, 6H), 3.75–3.93 (m, 1H), 6.14 (d, J = 5.5 Hz, 1H), 7.09 (d, J = 7.6 Hz, 2H), 7.20–7.38 (m, 4H), 7.41–7.50 (m, 1H), 7.51–7.58 (m, 1H), 8.10 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 25.0, 28.9, 33.2, 41.9, 72.4, 108.7, 120.1, 124.2, 126.4, 127.9, 128.1, 128.2, 128.3, 131.2, 137.8, 145.9, 174.1.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methoxybenzyl)pyrrolidin-2-one (**2.9d**). Yellow oil; ^{1}H NMR δ 2.35–2.60 (m, 1H), 2.63–2.89 (m, 2H), 2.97–3.18 (m, 1H), 3.45–3.63 (d, J = 15.3 Hz, 1H), 3.77 (s, 3H), 4.83 (d, J = 9 Hz, 1H), 6.33 (s, 1H), 6.67–6.85 (m, 2H), 6.90–7.10 (s, 2H), 7.18–7.35 (m, 1H), 7.35–7.56 (m, 2H), 8.00–8.21 (m, 1H); ^{13}C NMR δ 25.1, 29.4, 43.7, 55.1, 71.4, 109.0, 113.9, 120.3, 124.3, 126.8, 127.9, 129.6, 131.3, 146.3, 159.2, 174.0. Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 66.79; H, 5.64; N, 17.23.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methoxyphenethyl)-pyrrolidin-2-one (**2.9e**). Yellow oil; ^{1}H NMR δ 2.35–2.57 (m, 2H), 2.59–2.89 (m, 4H), 2.90–3.05 (m, 2H), 3.74 (s, 3H), 6.20 (d, J = 5.8 Hz, 1H), 6.81 (d, J = 7.4 Hz, 2H), 6.99 (d, J = 7.1 Hz, 2H), 7.30–7.38 (m, 1H), 7.41–7.48 (m, 1H), 7.51–7.53 (m, 1H), 8.09 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ 25.1, 29.2, 32.4, 42.2, 55.0, 72.7, 108.8, 113.9, 120.4, 124.3, 128.0, 129.4, 129.9,

131.3, 146.2, 158.2, 174.2 Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.65. Found: C, 67.58; H, 6.09; N, 16.62.

2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-5-oxo-1-pyrrolidinyl]ethyl acetate (**2.9f**) and 2-[2-(2*H*-1,2,3-Benzotriazol-2-yl)-5-oxo-1-pyrrolidinyl]ethyl acetate (**2.10f**). As a mixture; yellow oil; ^{1}H NMR δ 1.93 (s, 3H), 2.40–3.05 (m, 4H), 3.60–3.70 (m, 1H), 3.70–3.85 (m, 1H), 3.85–4.05 (m, 1H), 4.05–4.15 (m, 1H), 6.72 (d, J = 6.0 Hz, 0.8 H), 6.88 (d, J = 6.0 Hz, 0.2 H), 7.35–7.60 (m, 3H), 7.80–7.90 (m, 0.2H), 8.11 (d, J = 8.7 Hz, 0.8H); ^{13}C NMR δ 20.3, 25.1, 25.4, 25.8, 28.5, 28.9, 29.0, 39.7, 39.8, 42.8, 60.3, 61.2, 72.6, 73.0, 78.8, 108.8, 109.2, 120.2, 124.2, 124.3, 126.7, 126.8, 127.9, 128.1, 131.2, 131.7, 144.2, 145.8, 146.1, 170.4, 174.6, 175.1.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(3,4-dimethoxybenzyl)pyrrolidin-2-one (**2.9g**). Yellow oil; ^{1}H NMR δ 2.37–2.53 (m, 1H), 2.65–2.85 (m, 2H), 2.95–3.18 (m, 1H), 3.50–3.65 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.75–4.85 (m, 1H), 6.30–6.40 (m, 1H), 6.45–6.65 (m, 2H), 6.65–6.75 (m, 1H), 7.18–7.30 (m, 1H), 7.30–7.50 (m, 2H), 8.08 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ 24.7, 28.9, 43.9, 55.1, 55.3, 71.2, 108.7, 110.5, 110.8, 119.6, 120.2, 123.8, 126.8, 127.2, 130.9, 145.7, 147.9, 148.2, 173.7.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-[(1*S*)-1-phenylethyl]pyrrolidin-2-one (**2.9h**). Obtained as diastereoisomers in the ratio 57:43 (minor isomer in the parentheses); yellow oil; ^{1}H NMR δ 0.79 (d, *J* = 7.2 Hz, 3H), 2.26–2.38 (m, 1H), 2.53–2.77 (m, 2H), 3.12–3.30 (m, 1H), 5.50–5.65 (m, 1H), 6.05–6.15 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H),

7.15–7.25 (m, 2H), 7.30–7.53 (m, 5H), 8.10 (d, J = 7.6 Hz, 1H); ^{13}C NMR δ 15.8 (15.1), 26.8 (27.0), 29.7 (29.4), 50.2 (50.5), 69.9 (69.6), 109.3 (109.1), 120.4 (120.1), 124.3 (124.2), 127.6 (127.5), 127.8 (127.6), 128.2 (127.9), 128.9, 131.3, 138.5, 146.1 (147.2), 174.9 (175.2). Anal. Calcd for $C_{18}H_{18}N_4O$: C, 70.57; H, 5.92; N, 18.29. Found: C, 70.23; H, 6.02; N, 18.46.

Methyl (2*S*)-2-[2-(1*H*-1,2,3-benzotriazol-1-yl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (**2.9i**). Obtained as diastereoisomers in the ratio 59:41 (minor isomer in the parentheses); yellow oil; ^{1}H NMR δ 2.34–2.90 (m, 3H), 2.93–3.15 (m, 2H), 3.49 (d, J = 8.1 Hz, 1H), 3.66 (s, 3H) [3.41 (s, 3H)], 4.79–4.87 (m, 1H), 6.06 (d, J = 5.7 Hz, 1H) [6.30 (d, J = 6.6 Hz, 1H)], 7.00–7.10 (m, 4H), 7.23 (t, J = 6.6 Hz, 2H), 7.46 (t, J = 6.9 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H); ^{13}C NMR δ 26.1 (25.2), 28.7 (28.6), 34.1 (32.9), 52.3 (51.5), 55.9 (54.6), 78.3 (76.3), 103.4, 110.0 (112.8), 117.9 (117.8), 119.4 (120.2), 123.5 (121.9), 126.4 (126.2), 126.8 (126.5), 127.9 (127.8), 128.3 (128.2), 135.3 (132.2), 136.1 (135.8), 143.8 (145.4), 169.7 (169.1), 175.2 (175.3).

(2*S*)-2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-5-oxo-1-pyrrolidinyl]-2-phenylethyl acetate (**2.9j**). Obtained as diastereoisomers in the ratio 54:46 (minor isomer in the parentheses); yellow oil; ^{1}H NMR δ 1.95 (s, 3H) [1.75 (s, 3H)], 2.25–2.45 (m, 1H), 2.60–2.87 (m, 2H), 3.07–3.32 (m, 1H), 4.00–4.18 (m, 1H) [3.70–3.83 (m, 1H)], 4.48–4.57 (m, 1H) [5.05–5.18 (m, 1H)], 5.20–5.31 (m, 1H) [5.48–5.60 (m, 1H)], 6.67 (J = 6.3 Hz, 1H) [6.25 (d, J = 6.4 Hz, 1H)], 6.80–7.05 (m, 2H), 7.10–7.55 (m, 6H), 7.89 (d,

J = 8.2 Hz, 1H) [8.08 (d, J = 8.2 Hz, 1H)]; ^{13}C NMR δ 20.6 (20.3), 25.8 (26.3), 29.6 (29.5), 54.6 (54.2), 61.8 (61.3), 70.7 (71.0), 109.3 (109.2), 120.1 (120.5), 123.9, 124.3, 126.9 (127.4), 127.7, 127.8, 128.0 (128.7), 129.0, 130.8 (130.9), 134.2 (134.6), 146.3 (146.1), 170.0 (170.6), 175.2 (175.1).

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-[2-(2-pyridinyl)ethyl]pyrrolidin-2-one (**2.9k**). Brown oil; ^{1}H NMR δ 2.30–2.45 (m, 1H), 2.50–2.80 (m, 2H), 2.85–3.15 (m, 4H), 3.93–4.05 (m, 1H), 6.52 (d, J = 7.7 Hz, 1H), 7.05–7.20 (m, 2H), 7.40–7.70 (m, 4H), 8.09 (d, J = 8.1 Hz, 1H), 8.50–8.58 (m, 1H); ^{13}C NMR δ 25.6, 29.3, 35.4, 40.2, 72.6, 109.1, 120.4, 121.7, 123.3, 124.3, 128.1, 131.6, 136.5, 146.3, 149.1, 158.2, 174.7.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-benzylpyrrolidin-2-one (**2.10b**). Yellow oil; ^{1}H NMR δ 2.50–2.67 (m, 3H), 3.08–3.25 (m, 1H), 3.60, 4.94 (AB, J = 14.7 Hz, 2H), 6.22 (d, J = 6.6 Hz, 1H), 7.20–7.29 (m, 5H), 7.40–7.43 (m, 2H), 7.80–7.90 (m, 2H); ^{13}C NMR δ 25.9, 29.0, 44.4, 77.8, 118.4, 126.9, 127.8, 128.5, 128.6, 135.3, 144.4, 175.1.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-phenethylpyrrolidin-2-one (**2.10c**). Brown oil; ^{1}H NMR δ 2.40–2.70 (m, 4H), 2.89–3.21 (m, 3H), 3.78–3.95 (m, 1H), 6.11–6.20 (m, 1H), 7.10–7.40 (m, 5H), 7.40–7.52 (m, 2H), 7.84–7.87 (m, 2H); ^{13}C NMR δ 25.3, 28.5, 32.8, 41.9, 78.6, 117.9, 126.0, 126.5, 128.0, 128.1, 137.7, 143.9, 174.8. Anal. Calcd for $C_{18}H_{18}N_4O$: N, 18.29. Found: N, 17.98.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-(4-methoxybenzyl)pyrrolidin-2-one (**2.10d**).

Yellow oil; ^{1}H NMR δ 2.45–2.70 (m, 3H), 3.05–3.28 (m, 1H), 3.59 (d, *J* = 14.6 Hz, 1H), 3.73 (s, 3H), 4.83 (d, *J* = 14.4 Hz, 1H), 6.18–6.35 (m, 1H), 6.70–6.90 (m, 2H), 7.07–7.28 (m, 2H), 7.30–7.55 (m, 2H), 7.80–8.00 (m, 2H); ^{13}C NMR 25.7, 29.0, 43.7, 55.1, 77.6, 113.8, 118.3, 126.8, 127.2, 129.8, 131.5, 144.3, 159.0, 175.0. Anal. Calcd for $C_{18}H_{18}N_4O_2$: N, 17.38. Found: N, 17.43.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-(4-methoxyphenethyl)-pyrrolidin-2-one (**2.10e**).

Yellow oil; ^{1}H NMR δ 2.41–2.75 (m, 4H), 2.75–3.20 (m, 3H), 3.76 (s, 4H), 6.10–6.20 (m, 1H), 6.75–6.89 (m, 2H), 7.05–7.15 (m, 2H), 7.35–7.47 (m, 2H), 7.80–7.95 (m, 2H); ^{13}C NMR δ 25.8, 29.0, 32.3, 42.5, 55.1, 79.0, 113.8, 118.3, 126.9, 129.5, 130.1, 144.4, 158.2, 175.3. Anal. Calcd for $C_{19}H_{20}N_4O_2$: C, 67.84; H, 5.99; N, 16.65. Found: C, 67.65; H, 6.15; N, 16.70.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-(3,4-dimethoxybenzyl)pyrrolidin-2-one (**2.10g**).

Yellow oil; ^{1}H NMR δ 2.45–2.73 (m, 3H), 3.05–3.25 (m, 1H), 3.60, 4.83 (AB, *J* = 14.5 Hz, 2H), 4.80 (s, 6H), 6.21–6.30 (m, 1H), 6.67–6.81 (m, 3H), 7.40–7.50 (m, 2H), 7.83–7.92 (m, 2H); ^{13}C NMR δ 25.7, 29.0, 44.3, 55.7, 77.7, 110.7, 111.7, 118.2, 121.1, 126.8, 127.5, 144.3, 148.5, 148.8, 175.0.

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-[(1*S*)-1-phenylethyl]pyrrolidin-2-one (**2.10h**).

Yellow oil; Obtained as diastereoisomers in the ratio 53:47 (minor isomer in the

parentheses); ^{1}H NMR δ 0.79 (d, *J* = 7.2 Hz, 3H), 2.13–2.28 (m, 1H), 2.37–2.63 (m, 2H), 3.15–3.35 (m, 1H), 5.52–5.65 (m, 1H), 6.09–6.15 (m, 1H), 7.25–7.51 (m, 7H), 7.83–7.95 (m, 2H); ^{13}C NMR δ 15.3 (14.6), 27.3 (27.1), 29.1 (28.6), 50.1 (50.8), 76.5 (76.1), 118.3 (118.2), 126.7 (126.5), 127.4 (127.2), 127.9, 128.7, 138.9, 144.2 (144.7), 175.3 (175.0).

Methyl (2*S*)-2-[2-(2*H*-1,2,3-benzotriazol-2-yl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (**2.10i**). Obtained as diastereoisomers in the ratio 54:46 (minor isomer in the parentheses); brown oil; ^{1}H NMR δ 2.30–2.67 (m, 3H), 2.90–3.19 (m, 2H), 3.33 (d, *J* = 8.1 Hz, 1H), 3.41 (s, 3H) [3.66 (s, 3H)], 4.79–4.87 (m, 1H) [4.34–4.41 (m, 1H)], 5.98 (d, *J* = 6.9 Hz, 1H) [6.56 (d, *J* = 8.4 Hz, 1H)], 6.92–7.10 (m, 3H), 7.12–7.25 (m, 3H), 7.25–7.51 (m, 2H), 8.01 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ 25.1 (24.2), 28.7 (30.3), 34.1 (33.2), 51.6 (52.9), 55.9 (54.9), 72.0 (70.9), 109.1, 119.6 (2), 123.8 (123.7), 126.4 (126.2), 127.4 (126.5), 127.8 (127.5), 127.9 (2), 128.1 (128.0), 128.6, 131.1 (130.6), 136.1 (135.6), 145.7 (145.6), 169.2 (168.8), 174.5 (174.2).

(2*S*)-2-[2-(2*H*-1,2,3-Benzotriazol-2-yl)-5-oxo-1-pyrrolidinyl]-2-phenylethyl acetate (**2.10j**). Obtained as diastereoisomers in the ratio 52:48 (minor isomer in the parentheses); yellow oil; ^{1} H NMR 1.66 (s, 3H) [1.87 (s, 3H)], 2.35–2.75 (m, 3H), 3.17–3.42 (m, 1H), 3.90–4.12 (m, 1H), 4.48–4.62 (m, 1H) [5.01–5.17 (m, 1H)], 5.24–5.40 (m, 1H) [5.55–5.67 (m, 1H)], 6.22 (d, *J* = 7.0 Hz, 1H) [6.46 (d, *J* = 6.9 Hz, 1H)], 6.80–6.95 (m, 1H), 7.01–7.15 (m, 1H), 7.24–7.51 (m, 5H), 7.60–7.75 (m, 1H), 7.81–7.95 (m, 1H); ^{13}C NMR δ 20.2 (20.5), 27.3 (26.7), 29.3 (29.4), 54.9 (53.9), 61.9 (61.5), 77.4 (76.8), 118.3

(118.1), 126.6, 127.1, 127.3, 127.6, 127.7, 127.9, 128.6, 128.9, 134.7, 134.9, 144.3 (144.0), 170.6 (171.6), 176.1 (175.9).

5-(2*H*-1,2,3-Benzotriazol-2-yl)-1-[2-(2-pyridinyl)ethyl]pyrrolidin-2-one (**2.10k**). Brown oil; ^{1}H NMR δ 2.42–2.70 (m, 3H), 2.85–3.20 (m, 3H), 3.20–3.30 (m, 1H), 3.90–4.08 (m, 1H), 6.38–6.42 (m, 1H), 7.00–7.15 (m, 2H), 7.30–7.45 (m, 2H), 7.50–7.65 (m, 1H), 7.80–7.91 (m, 2H), 8.40–8.55 (m, 1H); ^{13}C NMR δ 25.9, 28.8, 35.3, 40.5, 78.9, 118.2, 121.4, 123.0, 126.7, 136.2, 144.2, 149.0, 158.2, 175.4.

1-(1-Benzyl-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**2.11a**). Yield: 3.0%; ^{1}H NMR δ: 5.14 (s, 2H), 6.59–6.60 (m, 1H), 6.80–6.81 (m, 1H), 7.15–7.16 (m, 1H), 7.21-7.25 (m, 2H), 7.32–7.39 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ: 54.1, 103.6, 110.4, 114.2, 119.9, 121.3, 122.2, 123.9, 127.3, 127.5, 128.1, 128.9, 132.7, 136.8, 145.8. Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.42; H, 5.15. Found: C, 74.21; H, 5.24.

1-(1-Benzyl-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**2.11b**). Yellow oil; ^{1}H NMR δ 5.14 (s, 2H), 6.59–6.60 (m, 1H), 6.80–6.81 (m, 1H), 7.15–7.16 (m, 1H), 7.21–7.25 (m, 2H), 7.32–7.39 (m, 4H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 54.1, 103.6, 110.4, 114.2, 119.9, 121.3, 122.2, 123.9, 127.3, 127.5, 128.1, 128.9, 132.7, 136.8, 145.8. Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.42; H, 5.15. Found: C, 74.21; H, 5.24.

1-(1-Phenethyl-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**2.11c**). Yellow oil; ^{1}H NMR δ 3.10 (t, *J* = 6.8 Hz, 2H), 4.17 (t, *J* = 6.8 Hz, 2H), 6.55–6.60 (m, 1H), 6.65–6.70 (m, 1H), 6.98–7.10 (m, 1H), 7.10–7.20 (m, 2H), 7.20–7.39 (m, 4H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 8.07 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 38.1, 51.8, 103.3, 110.4, 113.7, 119.7, 120.7, 121.6, 123.8, 126.8, 127.4, 128.6, 132.7, 137.8, 145.7. HRMS Calcd for $C_{18}H_{17}N_4$: 289.1453 (M+1), found: 289.1451.

1-{1-[(1*S*)-1-Phenylethyl]-*1H*-pyrrol-2-yl}-*1H*-1,2,3-benzotriazole (**2.11h**). Yellow oil; ^{1}H NMR δ 1.90 (d, *J* = 7.2 Hz, 3H), 5.82 (q, *J* = 7.2 Hz, 1H), 6.54–6.63 (m, 1H), 6.80–6.90 (m, 1H), 7.16–7.26 (m, 3H), 7.26–7.45 (m, 4H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ 21.8, 58.8, 103.0, 110.4, 112.7, 119.6, 121.8, 123.8, 125.9, 127.4, 127.8, 128.7, 132.6, 142.1, 145.7. HRMS Calcd for $C_{18}H_{17}N_4$: 289.1453 (M+1), found: 289.1451.

(2*S*)-2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-1*H*-pyrrol-1-yl]-2-phenyl-1-ethanol (**2.11j**). Yellow oil; ^{1}H NMR δ 2.07 (s, 3H), 4.72–4.78 (m, 2H), 5.50–5.59 (m, 1H), 6.64 (d, *J* = 1.4 Hz, 1H), 6.89 (s, 1H), 7.25–7.35 (m, 3H), 7.36–7.50 (m, 4H), 7.50–7.59 (m, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ 20.8, 62.3, 65.1, 103.7, 110.4, 111.1, 113.3, 120, 123, 126.7, 127.6, 128.8, 129.1, 136.8, 170.5. HRMS Calcd for $C_{20}H_{19}N_4O_2$: 347.1508 (M+1), found: 347.1525.

2.3.2 General Procedure for the Reaction of **2.9** with Allylsilanes

To an ice cold solution of **2.9** (0.7 mmol) in dry CH_2Cl_2 (10 mL) under N_2, was added an appropriate allylsilane (2.8 mmol) and stirred for 10 min. $BF_3{\cdot}Et_2O$ (4.2 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and the mixture was stirred at 0 °C for 24 h. Then 2 M NaOH (10 mL) was added to quench the reaction. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. After removal of solvents *in vacuo*, the residue was separated by column chromatography (silica gel) with hexane/EtOAc (3:2) as eluent to give **2.18**.

5-Allyl-1-benzyl-pyrrolidin-2-one (**2.18a**). Yellow oil; ^{1}H NMR δ 1.72–1.90 (m, 1H), 2.03–2.11 (m, 1H), 2.14–2.30 (m, 1H), 2.36–2.65 (m, 3H), 3.51–3.56 (m, 1H), 4.02 (d, J = 14.7 Hz, 1H), 5.02–5.17 (m, 3H), 5.60–5.73 (m, 1H), 7.20–7.48 (m, 5H); ^{13}C NMR δ 23.1, 30.0, 37.0, 44.1, 56.2, 118.7, 127.4, 127.8, 128.5, 132.4, 136.3, 175.4. HRMS Calcd for $C_{14}H_{18}NO$: 216.1388 (M+1), found: 216.1390.

5-Allyl-1-phenethyl-pyrrolidin-2-one (**2.18b**). Yellow oil; ^{1}H NMR δ 1.65–1.89 (m, 1H), 1.97–2.53 (m, 5H), 2.75–3.07 (m, 2H), 3.10–3.28 (m, 1H), 3.45–3.67 (m, 1H), 3.85–4.05 (m, 1H), 5.05–5.30 (m, 2H), 5.55–5.80 (m, 1H), 7.15–7.45 (m, 5H); ^{13}C NMR δ 23.4, 30.0, 33.7, 37.4, 41.9, 57.2, 118.7, 126.4, 128.4, 128.6, 132.7, 138.8, 175.0. HRMS Calcd for $C_{15}H_{20}NO$: 230.1545 (M+1), found: 230.1546.

5-(2-Methyl-2-propenyl)-1-phenethyl-pyrrolidin-2-one (**2.18c**). Yellow oil; ^{1}H NMR δ 1.66 (s, 3H), 1.83–2.10 (m, 2H), 2.25–2.61 (m, 4H), 2.75–3.00 (m, 2H), 3.12–3.30 (m, 1H), 3.45–3.60 (m, 1H), 3.87–4.05 (m, 1H), 4.71 (s, 1H), 4.83 (s, 1H), 7.10–7.50 (m, 5H); ^{13}C NMR δ 22.4, 23.8, 29.8, 33.9, 41.4, 42.1, 56.4, 113.6, 126.4, 128.5, 128.6, 138.7, 140.9, 175.4. HRMS Calcd for $C_{16}H_{22}NO$: 244.1701 (M+1), found: 244.1688.

1-(4-Methoxybenzyl)-5-(2-methyl-2-propenyl)pyrrolidin-2-one (**2.18d**). Yellow oil; ^{1}H NMR δ 1.64 (s, 3H), 1.70–1.80 (m, 1H), 1.91–2.10 (m, 2H), 2.30–2.60 (m, 3H), 3.50–3.60 (m, 1H), 3.80 (s, 3H), 3.94, 4.93 (AB, J = 14.7 Hz, 2H), 4.87 (d, J = 14.5 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 22.9, 24.1, 30.3, 41.7, 44.0, 55.5, 55.6, 113.9, 114.3, 114.4, 118.8, 127.3, 129.2, 129.7, 130.4, 141.7, 159.4, 175.3. HRMS Calcd for $C_{16}H_{22}NO_2$: 260.1651 (M+1), found: 260.1659.

5-Allyl-1-(4-methoxyphenethyl)-pyrrolidin-2-one (**2.18e**). Yellow oil; ^{1}H NMR δ 1.61–1.78 (m, 1H), 1.95–2.10 (m, 1H), 2.10–2.25 (m, 1H), 2.25–2.47 (m, 3H), 2.65–2.90 (m, 2H), 3.00–3.20 (m, 1H), 3.45–3.55 (m, 1H), 3.77 (s, 3H), 3.75–4.00 (m, 1H), 5.05–5.20 (m, 2H), 5.60–5.77 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H); ^{13}C NMR 23.2, 29.9, 32.6, 37.3, 41.9, 55.0, 57.0, 113.7, 118.5, 129.4, 130.6, 132.6, 158.0, 174.7. HRMS Calcd for $C_{16}H_{22}NO_2$: 260.1651 (M+1), found: 260.1676.

1-(4-Methoxyphenethyl)-5-(2-methyl-2-propenyl)pyrrolidin-2-one (**2.18f**). Yellow oil; ^{1}H NMR δ 1.68 (s, 3H), 1.68–1.80 (m, 1H), 1.90–2.10 (m, 2H), 2.20–2.50 (m, 3H),

2.70–2.90 (m, 2H), 3.00–3.20 (m, 1H), 3.40–3.60 (m, 1H), 3.70 (s, 3H), 3.80–4.00 (m, 1H), 4.73 (d, J = 8.5 Hz, 1H), 4.85 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 22.4, 23.8, 29.7, 33.0, 41.5, 42.0, 56.0, 56.1, 113.4, 113.7, 113.9, 129.5, 129.6, 141.1, 158.1, 174.7. HRMS Calcd for $C_{17}H_{24}NO_2$: 274.1807 (M+1), found: 274.1802.

Methyl (2*S*)-2-(2-allyl-5-oxo-1-pyrrolidinyl)-3-phenylpropanoate (**2.18g**). Yellow oil; ^{1}H NMR δ 1.50–1.90 (m, 2H), 2.00–2.60 (m, 4H), 2.70–2.90 (m, 1H), 3.30–3.50 (m, 2H), 3.76 (s, 3H), 4.05–4.20 (m, 1H), 5.00–5.20 (m, 2H), 5.40–5.80 (m, 1H), 7.10–7.50 (m, 5H); ^{13}C NMR δ 23.7, 29.5, 34.8, 37.8, 37.9, 52.4, 57.7, 59.6, 118.3, 126.7, 128.4, 129.1, 133.2, 170.3, 174.9. HRMS Calcd for $C_{17}H_{22}NO_3$: 288.1600 (M+1), found: 288.1588.

2.3.3 General Procedure for the Reaction of **2.9** with Organozinc Reagents

To an ice-cold solution of Grignard reagent (8.0 mmol) in dry THF (10 mL) under N_2, was added $ZnCl_2$ (8.5 mmol) and allowed to warm to room temperature over 0.5 h. A solution of **2.9b** or **2.9e** (2.7 mmol) in dry THF (10 mL) was then added and the reaction mixture was refluxed for 48 h. After cooling, CH_2Cl_2 (20 mL) and 2 M NaOH (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were dried over Na_2SO_4. After removal of solvents *in vacuo*, the residue was separated by column chromatography (silica gel) with hexane/EtOAc (3:2) as eluent to give **2.19a–g**.

1-Benzyl-5-(1-propynyl)-pyrrolidin-2-one (**2.19a**). Yellow oil; ^{1}H NMR δ 1.84 (s, 3H), 2.00–2.18 (m, 1H), 2.20–2.33 (m, 1H), 2.35–2.50 (m, 1H), 2.50–2.71 (m, 1H), 4.00–4.09 (m, 2H), 5.04 (d, J = 14.6 Hz, 1H), 7.26–7.31 (m, 5H); ^{13}C NMR δ 26.2, 30.0, 44.3, 48.6, 81.6, 127.4, 128.4, 128.5, 136.4, 174.0. HRMS Calcd for $C_{14}H_{16}NO$: 214.1232 (M+1), found: 214.1215.

1-(4-Methoxyphenethyl)-5-(1-propynyl)-pyrrolidin-2-one (**2.19b**). Yellow oil; ^{1}H NMR δ 1.83 (s, 3H), 1.90–2.10 (m, 1H), 2.15–2.30 (m, 1H), 2.30–2.40 (m, 1H), 2.40–2.55 (m, 1H), 2.70–2.90 (m, 2H), 3.20–3.35 (m, 1H), 3.77 (s, 3H), 3.80–3.90 (m, 1H), 4.05–4.15 (m, 1H), 6.82 (d, J = 7.7 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H); ^{13}C NMR δ 3.5, 26.8, 30.1, 32.8, 42.5, 49.9, 55.3, 76.9, 81.3, 114.0, 129.7, 130.9, 158.2, 174.2. HRMS Calcd for $C_{16}H_{20}NO_2$: 258.1494 (M+1), found: 258.1490.

1-(4-Methoxyphenethyl)-5-vinyl-pyrrolidin-2-one (**2.19c**). Colorless crystalline; mp 63–64 °C (from $CHCl_3$/hexane); ^{1}H NMR δ 1.60–1.80 (m, 1H), 2.10–2.20 (m, 1H), 2.20–2.50 (m, 2H), 2.60–2.90 (m, 2H), 3.00–3.20 (m, 1H), 3.78 (s, 3H), 3.70–3.90 (m, 2H), 5.16 (d, J = 17.0 Hz, 1H), 5.19 (d, J = 8.4 Hz, 1H), 5.50–5.70 (m, 1H), 6.82 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 25.5, 30.0, 32.7, 42.2, 55.1, 61.7, 113.7, 117.9, 129.7, 131.0, 137.8, 158.1, 174.8. Anal. Calcd for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.82.

1-(4-Methoxyphenethyl)-5-(1-propenyl)pyrrolidin-2-one (**2.19d**). Yellow oil; ^{1}H NMR δ 1.50–1.90 (m, 4H), 2.00–2.20 (m, 1H), 2.20–2.50 (m, 2H), 2.60–2.85 (m, 2H),

3.00–3.20 (m, 1H), 3.60–3.80 (m, 1H), 3.77 (s, 3H), 4.20–4.40 (m, 1H), 5.10–5.30 (m, 1H), 5.50–5.80 (m, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H); ^{13}C NMR δ 12.8, 25.6, 30.3, 32.8, 42.4, 54.8, 55.1, 113.7, 128.0, 129.5, 130.1, 130.9, 158.0, 174.7. HRMS Calcd for $C_{16}H_{22}NO_2$: 260.1651 (M+1), found: 260.1643.

5-Benzyl-1-(4-methoxyphenethyl)pyrrolidin-2-one (**2.19e**). Yellow oil; ^{1}H NMR δ 1.60–1.75 (m, 1H), 1.80–1.90 (m, 1H), 1.90–2.10 (m, 1H), 2.10–2.20 (m, 1H), 2.40–2.60 (m, 1H), 2.70–3.00 (m, 2H), 3.00–3.30 (m, 1H), 3.50–3.65 (m, 1H), 3.76 (s, 3H), 3.85–4.00 (m, 1H), 4.30–4.50 (m, 1H), 6.83 (d, J = 8.5 Hz, 2H), 7.02–7.20 (m, 3H), 7.20–7.40 (m, 4H); ^{13}C NMR δ 23.6, 24.6, 28.6, 29.6, 32.9, 33.0, 39.2, 42.0, 42.1, 55.0, 58.8, 68.1, 89.0, 113.7, 126.5, 127.5, 127.7, 128.4, 129.0, 129.4, 129.5, 130.7, 130.8, 136.8, 158.0, 174.8. HRMS Calcd for $C_{20}H_{24}NO_2$: 310.1807 (M+1), found: 310.1806.

5-Cyclopentyl-1-(4-methoxyphenethyl)pyrrolidin-2-one (**2.19f**). Yellow oil; ^{1}H NMR δ 1.40–1.80 (m, 8H), 1.80–2.00 (m, 1H), 2.00–2.40 (m, 2H), 2.40–2.60 (m, 1H), 2.70–2.90 (m, 2H), 3.10–3.35 (m, 1H), 3.60–3.80 (m, 1H), 3.78 (s, 3H), 3.80–3.90 (m, 1H), 4.64 (d, J = 5.9 Hz, 1H), 6.84 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.2 Hz, 2H); ^{13}C NMR δ 23.1, 25.9, 28.7, 32.3, 33.1, 33.2, 42.1, 55.1, 78.6, 88.5, 113.8, 129.5, 131.0, 158.1, 174.6. HRMS Calcd for $C_{18}H_{26}NO_2$: 288.1964, found: 288.1961.

1-(4-Methoxyphenethyl)-5-pentylpyrrolidin-2-one (**2.19g**). Colorless oil; ^{1}H NMR δ 0.90 (br s, 3H), 1.22–1.38 (m, 4H), 1.50–1.63 (m, 2H), 1.90–2.00 (m, 2H), 2.20–2.40

(m, 1H), 2.40–2.60 (m, 1H), 2.70–2.90 (m, 2H), 3.20–3.40 (m, 3H), 3.60–3.80 (m, 1H), 3.85 (s, 3H), 4.67–4.69 (m, 1H), 6.83 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H); ^{13}C NMR δ 13.9, 22.3, 24.6, 28.3, 28.9, 29.3, 33.1, 42.1, 55.1, 65.9, 89.5, 113.8, 129.5, 131.0, 158.1, 174.8. HRMS Calcd for $C_{18}H_{28}NO_2$: 290.2120 (M+1), found: 290.2101.

Diethyl 2-(5-oxo-1-phenethyl-2-pyrrolidinyl)malonate (**2.19h**). To freshly cleaned and dried Zn powder (1.56 g, 23.9 mmol) in THF (20 mL), was added diethyl 2-bromomalonate (0.75 g, 3.1 mmol) and allowed to reflux at 80 °C for one hour. A solution of **2.9e** (0.35 g, 1.04 mmol) in THF (20 mL) was then added dropwise over a period of 10 min. The solution was allowed to reflux for 48 h, cooled and quenched by 2M NaOH (20 mL). The mixture was extracted with 3 portions of CH_2Cl_2, dried over Na_2SO_4. After removal of solvents in vacuo, the residue was separated by column chromatography (silica gel) with hexane/EtOAc (3:1) as eluent to give **2.19h**.

Diethyl 2-(5-oxo-1-phenethyl-2-pyrrolidinyl)malonate (**2.19h**). Yellow oil; ^{1}H NMR δ 1.20–1.39 (m, 6H), 2.10–2.48 (m, 4H), 2.70–2.86 (m, 1H), 2.86–3.12 (m, 2H), 3.68 (d, J = 5.2 Hz, 1H), 3.90–4.05 (m, 1H), 4.10–4.30 (m, 5H), 7.10–7.40 (m, 5H); ^{13}C NMR δ 13.9, 21.5, 29.4, 33.3, 42.2, 53.5, 56.8, 61.7, 61.8, 126.4, 128.4, 128.6, 138.4, 166.9, 167.0, 175.1. Anal. Calcd for $C_{19}H_{25}NO_5$: N, 4.03. Found: N, 4.50.

2.3.4 General Procedure for the Reaction of **2.9** with Phosphorus Compounds

To a solution of **2.9** (1.3 mmol) in dry CH_2Cl_2 (20 mL) under N_2 at 0 °C, was added triethylphosphite (0.36 mL, 2.1 mmol) and $ZnBr_2$ (0.30 g, 1.3 mmol). The reaction mixture was stirred at 0 °C for 20 h, then quenched with 2 M NaOH (10 mL). The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4. After removal of solvent *in vacuo*, the residue was separated by column chromatography (silica gel) with hexane/EtOAc (4:1) as eluent to afford **2.20**.

Diethyl 1-(2-hydroxyethyl)-5-oxo-2-pyrrolidinylphosphonate (**2.20a**). Yellow oil; ^{1}H NMR δ 1.30–1.50 (m, 6H), 2.05 (s, 2H), 2.20–2.45 (m, 2H), 2.45–2.60 (m, 1H), 3.40–3.60 (m, 1H), 4.00–4.30 (m, 7H), 4.30–4.50 (m, 1H); ^{13}C NMR δ 16.3 (J = 5.4 Hz), 20.4 (J = 32.3 Hz), 29.3, 40.9, 52.9, 55.1, 60.9, 62.3 (J = 7.1 Hz), 62.9 (J = 7.0 Hz), 170.6, 175.4 (J = 3.3 Hz). HRMS Calcd for $C_{10}H_{21}NO_5P$: 266.1157 (M+1), found: 266.1162.

Diethyl 1-(4-methoxybenzyl)-5-oxo-2-pyrrolidinylphosphonate (**2.20b**). Yellow oil; ^{1}H NMR δ 1.35 (t, J = 8.1 Hz, 6H), 2.00–2.50 (m, 3H), 2.55–2.70 (m, 1H), 3.63 (d, J = 9.6 Hz, 1H), 3.80 (s, 3H), 4.10–4.30 (m, 5H), 5.17 (d, J = 14.4 Hz, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H); ^{13}C NMR δ 16.2 (J = 5.5 Hz), 16.3 (J = 5.3 Hz), 29.5, 44.4, 51.2, 53.4, 55.0, 55.3, 62.2 (J = 7.3 Hz), 62.9 (J = 7.1 Hz), 113.8, 127.7, 129.5,

158.9, 174.9 (J = 2.9 Hz). HRMS Calcd for $C_{16}H_{25}NO_5P$: 342.1470 (M+1), found: 342.1470.

Diethyl 1-(3,4-dimethoxybenzyl)-5-oxo-2-pyrrolidinylphosphonate (**2.20c**).

Yellow oil; ^{1}H NMR δ 1.36 (t, J = 6.9 Hz, 6H), 2.00–2.50 (m, 3H), 2.55–2.77 (m, 1H), 3.68 (d, J = 9.4 Hz, 1H), 3.86 (s, 6H), 4.10–4.30 (m, 5H), 5.16 (d, J = 14.7 Hz, 1H), 6.80–6.88 (m, 3H); ^{13}C NMR δ 16.2 (J = 5.5 Hz), 16.3 (J = 5.2 Hz), 20.1, 29.7, 44.9, 51.3, 53.5, 55.7 (J = 8.2 Hz), 62.5 (J = 7.3 Hz), 63.1 (J = 7.2 Hz), 110.8 (J = 38.7 Hz), 120.7, 128.0, 148.5 (J = 38.7 Hz), 175.1 (J = 2.9 Hz). HRMS Calcd for $C_{17}H_{27}NO_6P$: 372.1576 (M+1), found: 372.1597.

Diethyl 1-(4-methoxyphenethyl)-5-oxo-2-pyrrolidinylphosphonate (**2.20d**).

Yellow oil; ^{1}H NMR δ 1.33 (t, J = 6.9 Hz, 6H), 2.00–2.35 (m, 3H), 2.40–2.60 (m, 1H), 2.70–2.85 (m, 1H), 2.85–3.00 (m, 1H), 3.35–3.50 (m, 1H), 3.50–3.60 (m, 1H), 3.80 (s, 3H), 4.00–4.10 (m, 1H), 4.10–4.25 (m, 4H), 6.82 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 16.3 (J = 5.6 Hz), 16.4 (J = 5.2 Hz), 20.3, 29.5, 32.3, 43.5, 53.2, 55.0, 55.3, 62.0 (J = 7.0 Hz), 62.7 (J = 7.3 Hz), 113.7, 129.5, 130.4, 158.0, 174.9 (J = 3.0 Hz). HRMS Calcd for $C_{17}H_{27}NO_5P$: 356.1627 (M+1), found: 356.1627.

Diethyl 1-[(1*S*)-2-hydroxy-1-phenylethyl]-5-oxo-2-pyrrolidinylphosphonate (**2.20e**).

Yellow oil; ^{1}H NMR δ 1.30–1.40 (m, 6H), 2.00–2.40 (m, 2H), 2.43–2.65 (m, 1H), 2.70–3.10 (m, 2H), 3.40–3.60 (m, 3H), 4.00–4.30 (m, 4H), 7.20–7.45 (m, 5H); ^{13}C NMR δ 16.2 (J = 5.2 Hz), 16.3 (J = 5.1 Hz), 20.2, 29.5, 33.1, 43.3, 50.1, 53.1, 55.3, 62.1 (J =

7.3 Hz), 62.8 (J = 7.0 Hz), 126.3, 128.3, 128.5, 138.4 (J = 4.1 Hz), 175.0 (J = 3.1 Hz). Anal. Calcd for $C_{16}H_{24}NO_5P$: C, 56.30, H, 7.09, N, 4.10. Found: C, 55.83, H, 7.28, N, 4.49.

Methyl (2*S*)-2-[2-(diethoxyphosphoryl)-5-oxo-1-pyrrolidinyl]-3-phenylpropanoate (**2.20f**). Yellow oil; ^{1}H NMR δ 1.20–1.50 (m, 6H), 1.70–2.30 (m, 2H), 2.45–2.60 (m, 1H), 3.25–3.40 (m, 1H), 3.60–3.70 (m, 1H), 3.73 (s, 3H), 3.95–4.30 (m, 6H), 4.90–5.10 (m, 1H), 7.10–7.30 (m, 5H); ^{13}C NMR δ 16.2 (J = 6.6 Hz), 16.4 (J = 5.6 Hz), 20.6 (J = 2.6 Hz), 24.8 (J = 5.3 Hz), 29.5 (J = 12.5 Hz), 33.8, 34.6, 52.2, 52.6, 54.8, 55.0, 56.3, 57.2, 59.1, 62.0 (J = 7.1 Hz), 62.8 (J = 4.8 Hz), 63.1 (J = 4.6 Hz), 68.2, 70.4, 126.4, 126.8, 128.3, 128.5, 128.6, 129.0, 137.1, 137.8, 169.6, 170.3, 174.8, 176.7 (J = 5.0 Hz). HRMS Calcd for $C_{18}H_{27}NO_6P$: 384.1576 (M+1), found: 384.1574.

CHAPTER 3
SYNTHESES OF PYRROLO- AND INDOLO-ISOQUINOLINONES BY INTRAMOLECULAR CYCLIZATIONS OF 1-ARYLETHYL-5-BENZOTRIAZOLYL-PYRROLIDIN-2-ONES AND 3-BENZOTRIAZOLYL-2-ARYLETHYL-1-ISOINDOLINONES

3.1 Introduction

Our ongoing work with 5-(benzotriazolyl)pyrrolidin-2-ones [00JOC4364] has led to novel routes to polycyclic ring systems, such as 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**3.1**) and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.7**), both of which are of interest as natural products and biologically active compounds.

Three principal routes have been reported for the synthesis of **3.1** (Figure 3.1):

A. C3-C4 bond formation via the reduction of the intermediates **3.2**, obtained by 1,3-dipolar cycloadditions of nitrones **3.3** with electron-deficient ethylenes [88T3735] or acetylenes [63TL2019, 63TL2023];

B. C3-C4 bond formation by the intramolecular condensation of **3.4** with the elimination of H_2O [74BCSJ1023, 88H2403]; and importantly,

C. C10a-C10b bond formation from the cyclization of a transient *N*-acyliminium ion, generated either by the protonation of the C-C double bond of an

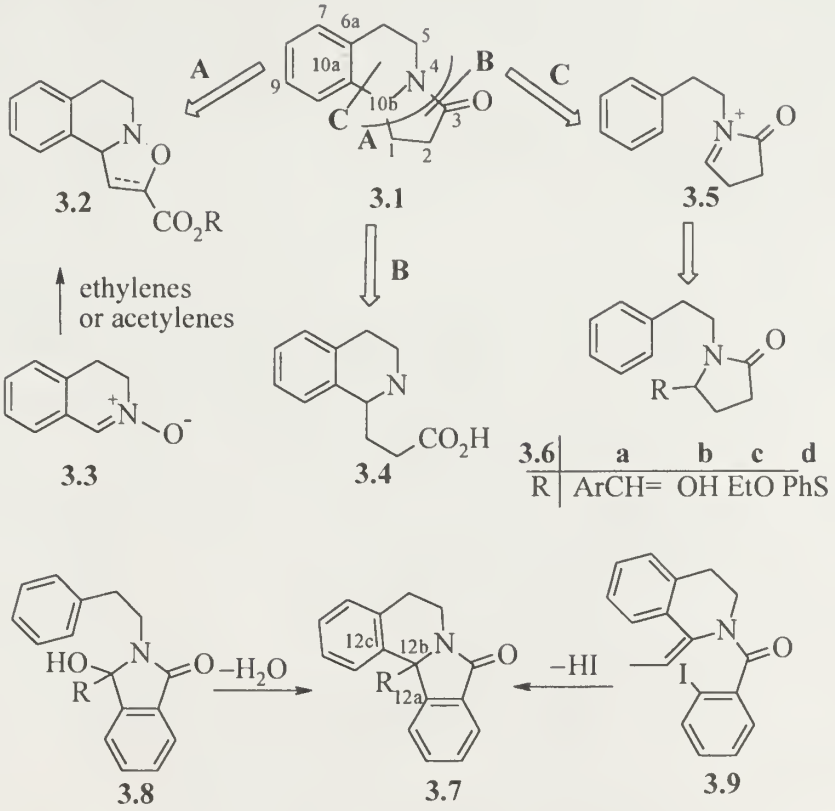
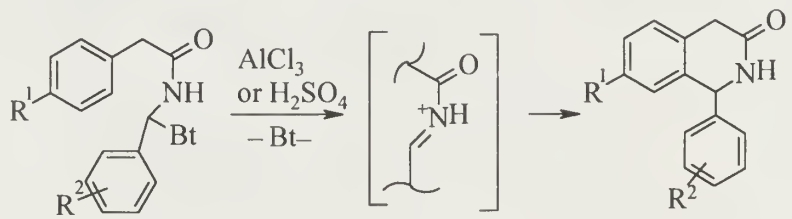


Figure 3.1

enamide **3.6a** [87JOC5662] or by the elimination of a hydroxy group from **3.6b**, [79TL3797, 95JOC7149, 95T4701, 97SC2817, 97JOC2080, 96TL7841] ethoxy group from **3.6c**, [89JA2487, 86JOC1341, 95SC1947, 83JOC5062] or phenylthio group from **3.6d** [98TL8585]. In recent work [00JOC235], treatment of amido-substituted thioacetals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) afforded both five- and six-membered alkylthio-substituted lactams **3.6** (R = CH_3S, EtS or PhS). Compounds **3.6** were produced *via* *N*-acyliminium ion **3.5** as transient intermediates, which subsequently cyclized with the tethered aromatic ring to produce an azapolycyclic ring. Ring system **3.7**

has been produced either by the acid-catalyzed cyclodehydration of α-hydroxy lactams **3.8** [97JOC2080, 90JCS(P1)1757] or by the catalytic cyclization of enamides **3.9**. [90T4003].

Most of the reported methods need at least three steps to reach the fused ring systems **3.1** or **3.7**. Our research group previously reported intramolecular cyclizations of *N*-(α-benzotriazolylalkyl)arylacetamides **3.10** (readily obtained from benzotriazole, an amide and an aldehyde [88JCS(PT1)2339]) to 1-aryl-1,4-dihydro-3-isoquinolinones **3.12** [93JHC381]. These reactions involve the *N*-acyliminium cation **3.11** formed by loss of the benzotriazolyl anion from **3.10** in the presence of $AlCl_3$ or H_2SO_4 (Figure 3.2). We now extend the benzotriazole methodology to prepare, in two steps, the ring systems **3.1** and **3.7**, which are generally obtained in high yields.



3.10 **3.11** **3.12**

Figure 3.2

3.2 Results and Discussion

3.2.1 Syntheses of 1-Arylethyl-5-(Benzotriazolyl)Pyrrolidin-2-Ones (3.15a-b) and (3.15d-e)

1-Arylethyl-5-(benzotriazolyl)pyrrolidin-2-ones (**3.15a-b**) and (**3.15d-e**) were readily prepared by the intermolecular condensations of 1-arylethylamines **3.13**, 2,5-dimethoxy-2,5-dihydrofuran (**3.14**) and benzotriazole in refluxing acetic acid (Figure 3.3). However, when the 1-arylethylamine **3.13c** was condensed with **3.14** and benzotriazole, **3.15c** was not detected, but instead the cyclized product **3.17c** was directly obtained in 95% yield (see discussion in the following paragraph). The nucleophilic replacement of a Bt group from analogues of **3.15** with allylsilanes, organozinc reagents or triethyl phosphite gave novel 1,5-disubstituted pyrrolidin-2-ones in good to excellent yields. [00JOC4364] The ^{1}H NMR and ^{13}C NMR spectra of **3.15a-b** and **3.15d-e** show that they are mixtures of the Bt^1 and Bt^2 isomers. It is well established, [97JOC8210, 98CR409, 99JOC7618] that both Bt^1 and Bt^2 are good leaving groups in the presence of Lewis acids such as $ZnBr_2$, $AlCl_3$, $TiCl_4$, BF_3 *etc*, and since the removal of this benzotriazolyl group from Bt^1 and Bt^2 isomers results in the same intermediate iminium cation **3.16**, the same products are obtained as when **3.15** is reacted with a nucleophile. Therefore, the crude intermediates **3.15a-b** and **3.15d-e**, which are mixtures of the Bt^1 and Bt^2 isomers, were used directly for the subsequent cyclization reaction.

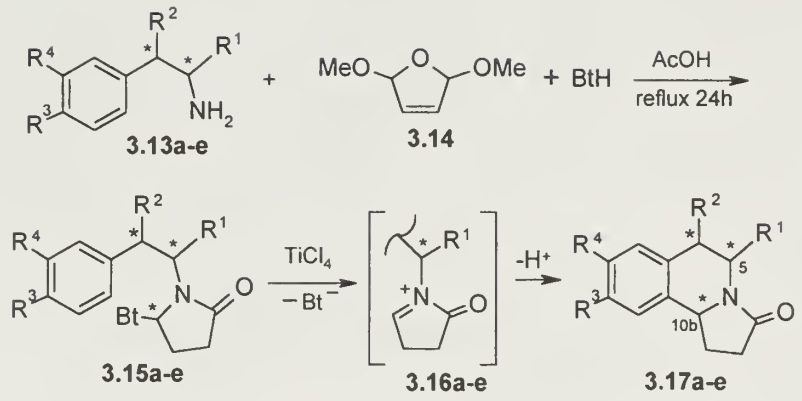


Figure 3.3

Table 3.1 Yields of **3.17a-e**.

No	R^1	R^2	R^3	R^4	**3.15**[a]	**3.17**[b]
a	H	H	H	H	94	75
b	H	H	OMe	H	96	80
c	H	H	OMe	OMe	[c]	95[d]
d	(*S*)-CO_2Me	H	H	H	78	83
e	(*S*)-Me	(*S*)-OH	H	H	95	40

[a] Yield for total Bt^1 and Bt^2 isomers based on the corresponding amine **3.13**.

[b] Isolated yield based on the intermediate **3.15**.

[c] No detectable amount of **3.15c** was isolated. Instead, a one-pot reaction of **3.13c**, **3.14** and BtH produced **3.17c** in 95% yield.

[d] An isolated yield of 52% was obtained from a one-pot reaction of **3.13c** and **3.14** in the absence of BtH.

3.2.2 Syntheses of 1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]Isoquinolin-3(2*H*)-Ones (3.17) by Cyclization of 3.15

Treatment of 1-arylethyl-5-(benzotriazolyl)pyrrolidin-2-ones (**3.15a-b**) or (**3.15d-e**) with 1.5 equiv of $TiCl_4$ in refluxing toluene for 24 h furnished 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones (**3.17a-b**) or (**3.17d-e**) in good to excellent yields. In addition, **3.17** was obtained by a one-pot reaction of **3.13c**, **3.14** and benzotriazole (Table 3.1, Figure 3.3). The structures of **3.17a-e** were confirmed by ^{1}H, ^{13}C NMR spectra and HRMS analyses. The correct number of aromatic tertiary carbon peaks in ^{13}C NMR spectra clearly show that the cyclized products **3.17a-e** are formed.

The yields of **3.17a**, **3.17b** and **3.17c** (with none, one and two methoxy groups on the benzene ring) are 75%, 80% and 95%, respectively. As expected, the presence of an increasing number of methoxy groups raises the electron density of the benzene ring, which in turn facilitates the intramolecular nucleophilic attack on the iminium cation **3.16**. Although 8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3.17c**) was produced in one step in 52% yield in the absence of benzotriazole, [97SC2817] its yield increased to 92% (also in one step based on amine **3.13c**), using the benzotriazole methodology. We believe that in the presence of benzotriazole, **3.15c** is again the transient intermediate and which then readily eliminates the benzotriazole anion in the presence of acetic acid (role similar to that of a Lewis acid) to form the iminium cation **3.16c**.

When chiral amines **3.13d** and **3.13e** were used, the 5-position of the pyrrolidin-2-one ring of **3.15d** and **3.15e** becomes a new chiral center. Elimination of the benzotriazolyl group from **3.15d** and **3.15e**, in the presence of titanium chloride, leads to

an identical iminium cation **3.16** in spite of the possible different stereochemistries at the 5-position of **3.15**. Determination of the absolute configuration at the 5-position of **3.15d** and **3.15e** is not relevant because of subsequent transformations.

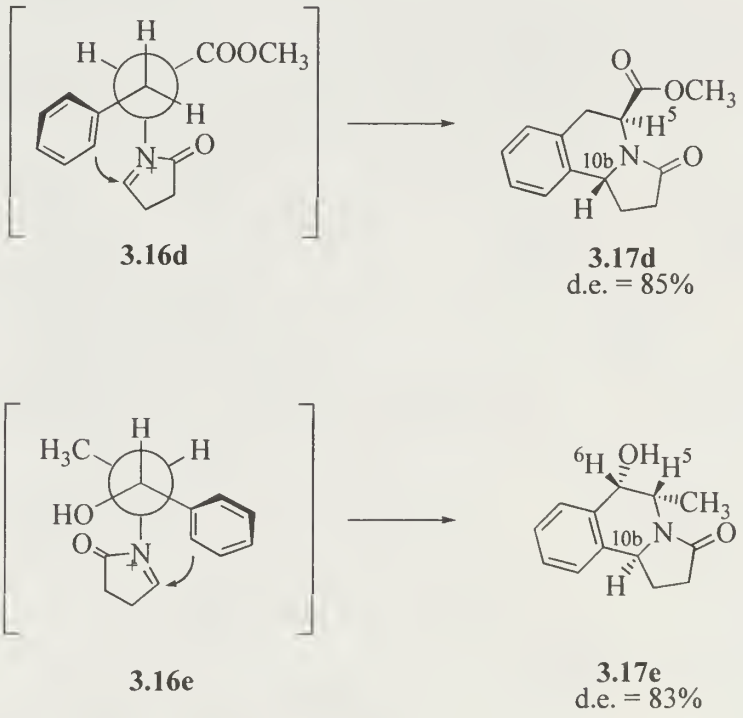


Figure 3.4

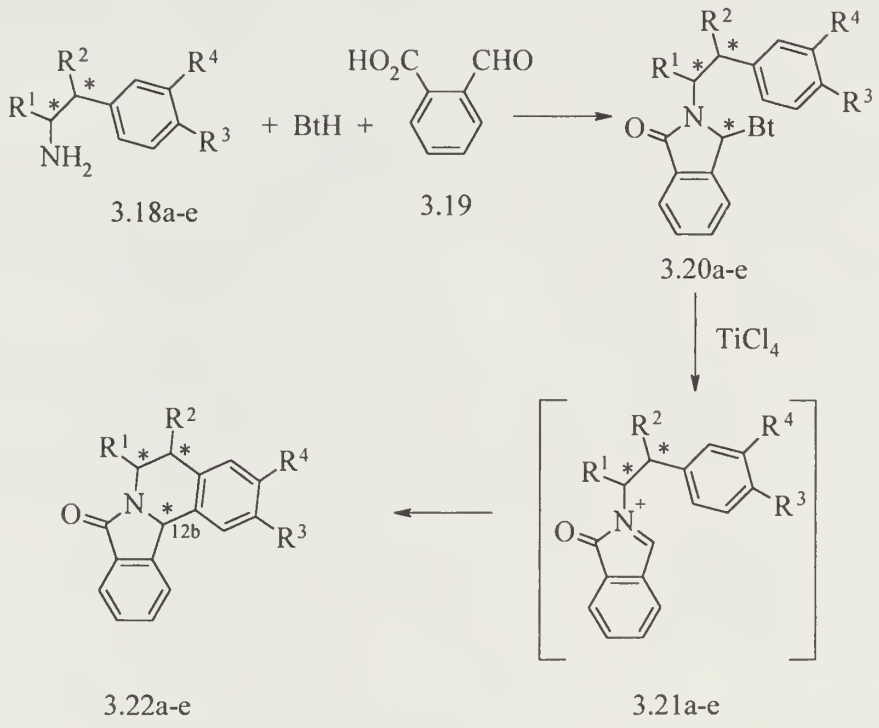
The 10b position of the cyclized product **3.17d-e** is also a new chiral center. The d.e. values of **3.17d** and **3.17e** as determined by ^{1}H NMR spectra of the crude products, were 85% and 83%, respectively. After separation on a column (silica gel), the ^{1}H and ^{13}C NMR spectra show that **3.17d** and **3.17e** were obtained as enantiomers. The absolute configuration at the 10b position for **3.17d** and **3.17e** was further determined by NOE experiments. When the proton peak at the 10b position of **3.17d** was irradiated, no

significant NOE effect was observed for H(5). This meant that H(10b) and H(5) are located *trans* to each other. For **3.17e**, H(6) appears as a doublet at 5.06 ppm and H(5) as a multiplet at 4.57 ppm, and these hydrogens are *cis* to each other as confirmed by their strong NOE effect. When H(5) at 4.57 ppm of **3.17e** was irradiated, there was no NOE effect between H(5) and H(10b) (5.66 ppm as multiplet). This result again indicates a *trans*-position between H(5) and H(10b). Thus, both **3.17d** and **3.17e** were obtained as single diastereoisomers, and this result is rationalized by the stereochemical conformations shown in Figure 3.4. Treatment of Bt intermediates **3.15d** and **3.15e** with titanium chloride led to the transition states **3.16d** and **3.16e**. Because of the steric repulsion between the ester and the phenyl groups of **3.16d**, the ester group prefers to be located at the *anti*-position to the phenyl group and thus induces the phenyl group to attack the iminium cation **3.16d** preferentially from the *anti*-direction to the ester group resulting in the major diastereoisomer **3.17d**. Similarly, the methyl group of **3.16e** also induces the phenyl group to attack the iminium cation **3.16e** from an *anti*-direction to the methyl group to give **3.17e**.

3.2.3 Syntheses of 3-Benzotriazolyl-2-Arylethyl-1-Isoindolinones (3.20a-e)

The intermolecular condensations of arylethylamines **3.18**, benzotriazole and 2-carboxybenzaldehyde (**3.19**) in refluxing toluene for 24 h using a Dean-Stark apparatus generated the 3-benzotriazolyl-2-arylethyl-1-isoindolinones (**3.20a-e**). The ^{1}H NMR and ^{13}C NMR spectra also show that **3.20a-e** were obtained as mixtures of the Bt^{1} and Bt^{2} isomers. Based on our previous work, the crude intermediates **3.20a-e**, which were

mixtures of the Bt^1 and Bt^2 isomers, could be used directly for the subsequent cyclizations.



3.18a-e 3.19 3.20a-e

3.22a-e 3.21a-e

Figure 3.5

Table 3.2 Yields of **3.21a-e**.

No	R^1	R^2	R^3	R^4	**3.20**[a]	**3.22**[b]
a	H	H	H	H	94	50
b	H	H	OMe	H	96	65
c	H	H	OMe	OMe	94	75
d	H	(*S*)-CH_2O H	H	H	92	60
e	(*S*)-CH_3	(*S*)-OH	H	H	92	65

[a] Yield based on the corresponding amines **3.18**.
[b] Isolated yield based on the intermediate **3.20**.

3.2.4 Syntheses of 5,12b-Dihydroisoindolo[1,2-*a*]Isoquinolin-8(6*H*)-Ones (3.22a-e) by Cyclization of 3.20a-e

Treatment of **3.20a-e** with 1.5 equiv of $TiCl_4$ in refluxing toluene produced 5,12b-dihydroisoindolo[2,1,*a*]isoquinolin-8(6*H*)-ones (**3.22a-e**) in good yields (Table 3.2) (Figure 3.5). The singlet peak for H(12b) (from 5.54 to 6.62 ppm) in ^{1}H NMR spectra and the correct number for tertiary aromatic carbon peaks in ^{13}C NMR spectra confirm the formation of the cyclized product **3.22a-e**. As expected, the introduction of methoxy groups improves the yield from 50% (for **3.22a**) to 65% (for **3.22b**) and further to 75% (for **3.22c**) due to their strong electron-releasing role.

Using chiral amines **3.18d** and **3.18e** as starting materials, ^{1}H and ^{13}C NMR spectra show that the final cyclized products **3.22d** and **3.22e** were isolated as enantiomers. For **3.22d**, although no strong NOE effect was observed between H(5) and H(12b), it is not possible to conclude that these hydrogens are in the *trans*-position to each other because of the large spatial distance between them. In addition, **3.22d** is a brown oil and thus its stereochemistry could not be determined by X-ray analysis. However, according to Cram's rule, the conformation **A** in the transition state **3.21d** should be more stable than the conformation **B**, since a large repulsion exists between the hydroxymethyl group and the iminium cation ring in conformation **B**. Therefore, cyclization of **3.21d** in the more stable conformation **A** probably leads to the major product **3.22d**, with H(5) and H(12b) at a *cis*-position (Figure 3.6).

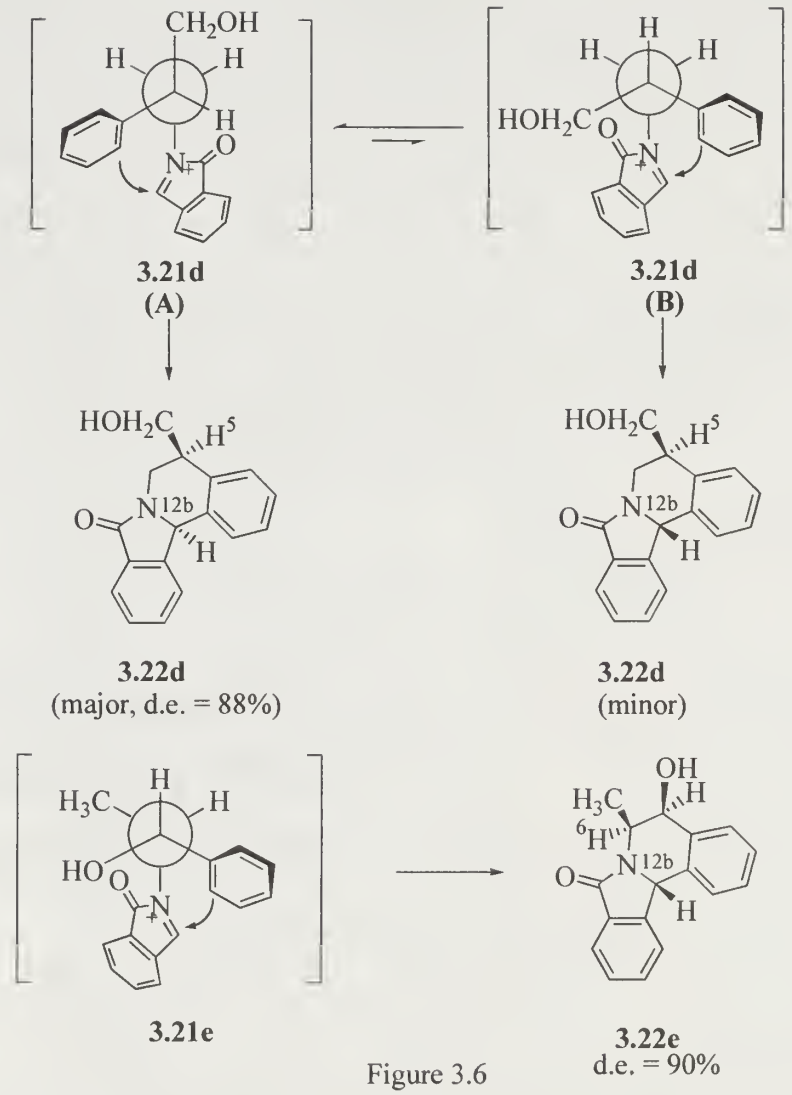


Figure 3.6

The absolute configuration of the new chiral center at the 12b-position of **3.22e** was determined by NOE experiments. When H(12b) (6.22 ppm as singlet) was irradiated, no significant NOE effect was detected for H(6) (4.67 ppm as multiplet). This result proved that there is a *trans*-position between H(12b) and H(6). This is reasonable as one expects the phenyl group to preferentially attack the iminium cation **3.21e** from an *anti*-direction to the methyl group, as shown in Scheme 6.

In summary, we have developed a simple and efficient route to the fused ring systems 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones (**3.17a-b**), (**3.17d-e**) and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones (**3.22a-e**) by titanium chloride induced intramolecular cyclizations of 1-arylethyl-5-benzotriazolyl-pyrrolidin-2-ones (**3.15a-b**), (**3.15d-e**) and 3-benzotriazolyl-2-arylethyl-1-isoindolinones (**3.20a-e**) respectively, which in turn were readily available in a single step from 1-arylethylamines, benzotriazole and either 2,5-dimethoxy-2,5-dihydrofuran (**3.14**) or 2-carboxybenzaldehyde (**3.19**). High stereoselectivity was observed in products prepared from chiral amines.

3.3 Experimental Section

Melting points were determined on a hot-stage apparatus without correction. Column chromatography was carried out on silica gel (230-400 mesh). The ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solution (300 MHz and 75 MHz respectively), with TMS or $CDCl_3$ as internal references.

3.3.1 General Procedure for the Preparation of 1-Arylethyl-5-(Benzotriazolyl)Pyrrolidin-2-Ones (**3.15a-b**) and (**3.15d-e**)

2,5-Dimethoxy-2,5-dihydrofuran (**3.14**, 2.89 g, 22 mmol), an appropriate amine **3.13a-e** (22 mmol) and benzotriazole (5.81 g, 48 mmol) were dissolved in acetic acid (20 mL) and refluxed under N_2 for 24 h. After cooling, 2 M NaOH (20 mL) was added and the mixture was extracted with CH_2Cl_2. The organic phase was dried over anhydrous

Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column (silica gel) with hexane/EtOAc (from 5:1 to 3:1) as an eluent to give **3.15a-b** and **3.15d-e** as a mixture of Bt^1 and Bt^2 isomers, which were used for the subsequent cyclizations. However, the reaction of **3.13c**, **3.14** and benzotriazole did not afford **3.15c**, but directly produced **3.17c** in 95% yield.

3.3.2 General Procedure for the Preparation of 1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]Isoquinolin-3(2*H*)-Ones (**3.17**) by Cyclization of **3.15**

To a stirred solution of **3.15a-b** or **3.15d-e** (2 mmol, a mixture of Bt^1 and Bt^2 isomers) in toluene (20 mL) under N_2, was added $TiCl_4$ (3 mmol) and refluxed for 24 h. The cooled dark solution was quenched with 2 M NaOH (20 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was separated by column (silica gel) with hexane/EtOAc (7 : 3) as an eluent to give **3.17a-b** or **3.17d-e**.

In a separate reaction with **3.17c** without use of benzotriazole, 2,5-dimethoxy-2,5-dihydrofuran (**3.14**, 0.33 g, 2.5 mmol) and 3,4-dimethoxybenzylamine (**3.13c**, 0.45 g, 2.5 mmol) were added to acetic acid (10 mL) and refluxed under N_2 for 24h. After cooling, CH_2Cl_2 was added and the organic phase was washed with 2 M NaOH and dried over anhyd Na_2SO_4. After removal of solvent *in vacuo*, the residue was separated by flash chromatography on silica gel using hexane/EtOAc (7 : 3) as an eluent to give 8,9-dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3.17c**) in 52% yield. However, when the reaction was carried out in the presence of benzotriazole, **3.17c** was obtained in a single step and in an increased yield of 95% based on **3.13c.**

1,5,6,10b-Tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**3.17a**) [95JOC7149]. Yellow oil; ^{1}H NMR δ 1.71–2.00 (m, 2H), 2.40–3.18 (m, 5H), 4.20–4.38 (m, 1H), 4.79 (t, *J* = 7.6 Hz, 1H), 7.05–7.35 (m, 4H); ^{13}C NMR 27.5, 28.5, 31.8, 37.0, 56.7, 124.8, 126.8, 126.9, 129.1, 133.5, 137.5, 173.2 (C=O).

9-Methoxy-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**3.17b**). Yellow oil; ^{1}H NMR δ 1.80–2.00 (m, 1H), 2.42–2.80 (m, 4H), 2.80–2.98 (m, 1H), 2.98–3.15 (m, 1H), 3.80 (s, 3H), 4.20–4.35 (m, 1H), 4.75 (t, *J* = 7.7 Hz, 1H), 6.63 (s, 1H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR 27.3, 27.6, 31.6, 37.1, 55.2, 56.8, 109.9, 112.5, 125.4, 129.9, 138.4, 158.3, 173.1 (C=O). HRMS Calcd. for $C_{13}H_{15}NO_2$: 218.1181 (M+1). Found: 218.1158.

8,9-Dimethoxy-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**3.17c**) [97SC2817]. Colorless needles (from $CHCl_3$/Et_2O); mp 104–105 °C (mp 104 °C); ^{1}H NMR δ 1.75–1.92 (m, 1H), 2.40–2.75 (m, 4H), 2.83–3.11 (m, 2H), 3.86 (s, 6H), 4.25–4.37 (m, 1H), 4.70–4.80 (m, 1H), 6.58 (s, 1H), 6.63 (s, 1H); ^{13}C NMR δ 27.6, 27.9, 31.6, 36.9, 55.8, 55.9, 56.4, 107.5, 111.5, 125.4, 129.2, 147.8, 148.0, 173.0 (C=O). HRMS Calcd. for $C_{14}H_{17}NO_3$: 248.1287 (M+1), found: 248.1287.

Methyl (5*S*, 10b*R*)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carboxylate (**3.17d**). Yellow oil; $[\alpha]_D^{25}$ = + 0.1 (c 1.2, $CHCl_3$); ^{1}H NMR δ 1.80–2.05 (m, 1H), 2.45–2.62 (m, 1H), 2.62–2.82 (m, 2H), 3.20–3.35 (m, 2H), 3.69 (s, 3H), 5.00–5.20 (m, 2H), 7.05–7.35 (m, 4H); ^{13}C NMR δ 27.6, 30.5, 31.4, 49.2, 52.4, 54.7, 124.7, 127.1, 127.2, 129, 130.8, 136.6, 170.9, 173.7. HRMS Calcd. for $C_{14}H_{15}NO_3$: 246.1130 (M+1), found: 246.1129.

(5*S*, 6*S*)-6-Hydroxy-5-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**3.17e**). Yellow oil; $[\alpha]_D^{25}$ = + 4.3 (c 2.0, $CHCl_3$); ^{1}H NMR δ 0.76 (d, *J* = 7.2 Hz, 3H), 2.04–2.11 (m, 1H), 2.40–2.79 (m, 4H), 4.50–4.60 (m, 1H), 5.06 (d, *J* = 5.7 Hz, 1H), 5.64–5.68 (m, 1H), 7.25–7.38 (m, 4H); ^{13}C NMR δ 14.3, 27.6, 31.9, 54.3, 81.9, 90.7, 110.1, 126.0, 127.7, 128.3, 137.2, 154.7, 178.2 (C=O).

3.3.3 General Procedure for the Preparation of 3-Benzotriazolyl-2-Arylethyl-1-Isoindolinones (**3.20a-e**)

2-Carboxybenzaldehyde (**3.19**, 1.50 g, 10 mmol), an appropriate amine **3.18a-e** (10 mmol) and benzotriazole (1.79 g, 15 mmol) were dissolved in toluene and refluxed under N_2 for 24 h with a Dean-Stark apparatus. After cooling, the toluene was removed in vacuo. Then, 2 M NaOH (20 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of solvent *in vacuo*, the residue was separated by column (silica gel) with hexane/EtOAc (from 5/1 to 3/1) as an eluent to give **3.20a-e** as mixtures of Bt^1 and Bt^2 isomers, which were used as such for the subsequent cyclizations.

3.3.4 General Procedure for the Preparation of 5,12b-Dihydroisoindolo[1,2-*a*]Isoquinolin-8(6*H*)-Ones (**3.22a-e**) by Cyclization of (**3.20a-e**)

To a stirred solution of **3.20a-e** (2 mmol, a mixture of Bt^1 and Bt^2 isomers) in toluene (20 mL) under N_2, was added $TiCl_4$ (3 mmol) and refluxed for 24 h. The cooled dark solution was quenched with 2 M NaOH (20 mL) and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent

in vacuo, the residue was separated by column (silica gel) with hexane/EtOAc (7 : 3) as an eluent to give **3.22a-e**.

5,12b-Dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.22a**) [68JOC3779]. Colorless needles; mp 114–116 °C (mp 114–116 °C); ^{1}H NMR δ 2.87–2.94 (m, 1H), 3.04–3.15 (m, 1H), 3.50–3.59 (m, 1H), 4.36–4.44 (m, 1H), 5.69 [s, 1H, H(12b)], 7.10–7.16 (m, 2H), 7.19–7.22 (m, 1H), 7.50 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.58–7.64 (m, 2H), 7.89 (dd, *J* = 7.2, 7.2 Hz, 2H); ^{13}C NMR δ 29.4, 38.3, 59.2, 123.5, 123.9, 125.1, 126.7, 127.5, 128.6, 129.2, 131.6, 132.7, 134.2, 134.7, 144.1, 168.2 (C=O).

2-Methoxy-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.22b**). Yellow oil; ^{1}H NMR δ 2.83 (dt, *J* = 15.6, 4.5 Hz, 1H), 2.95–3.05 (m, 1H), 3.44–3.82 (m, 1H), 3.82 (s, 3H), 4.36–4.44 (m, 1H), 5.64 [s, 1H, H(12b)], 6.79 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.10–7.16 (m, 2H), 7.50 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.61 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.85 (dd, *J* = 7.5, 2.4 Hz, 2H); ^{13}C NMR 28.5, 38.4, 55.4, 59.2, 111.4, 112.5, 123.4, 123.9, 126.8, 128.5, 130.1, 131.5, 132.8, 135.3, 144.0, 158.3, 167.9 (C=O). HRMS Calcd. for $C_{17}H_{16}NO_2$: 266.1181 (M+1), found: 266.1137.

2-(Methyloxy)-3-[(methyloxy)methyl]-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.22c**) [85TL2925]. Colorless needles (from diethyl ether); mp 172–173 °C (mp 173 °C); ^{1}H NMR δ 2.72–2.77 (m, 1H), 2.93–3.03 (m, 1H), 3.35–3.44 (m, 1H), 3.84 (s, 3H), 3.93 (s, 3H), 4.45–4.49 (m, 1H), 5.59 [s, 1H, H(12b)], 6.66 (s, 1H), 7.12 (s, 1H), 7.47 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.84 (dd, *J* = 6.9, 6.9 Hz, 2H); ^{13}C NMR δ 28.8, 38.0, 55.7, 56.0, 58.8, 108.5, 111.8, 122.9, 123.7, 125.8, 126.7, 128.2, 131.4, 132.5, 144.4, 147.6, 148.1, 167.7 (C=O).

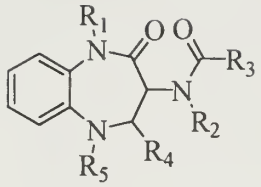
(5*S*, 12b*S*)-5-(Hydroxymethyl)-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.22d**). Brown oil; $[\alpha]_D^{25}$ = – 27.1 (c 1.3, $CHCl_3$); ^1H NMR δ 2.95–3.14 (m, 2H), 3.86–3.92 (m, 1H), 4.03–4.14 (m, 1H), 4.20–4.28 (m, 1H), 4.72 (br s, 1H), 5.54 [s, 1H, H(12b)], 7.15–7.40 (m, 4H), 7.49 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.64 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR δ 30.9, 53.1, 58.7, 65.7, 123.5, 124.0, 124.2, 126.6, 128.0, 128.2, 128.5, 131.3, 132.5, 133.9, 135.2, 142.5, 169.5 (C=O). HRMS Calcd. for $C_{17}H_{16}NO_2$: 266.1181 (M+1), found: 266.1173.

(5*S*,6*S*,12b*R*)-5-Hydroxy-6-methyl-5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (**3.22e**). Yellow oil; $[\alpha]_D^{25}$ = – 8.0 (c 1.6, $CHCl_3$); ^1H NMR δ 0.94 (d, *J* = 7.2 Hz, 3H), 4.67 (dq, *J* = 5.7, 5.7 Hz, 1H), 5.00 (d, *J* = 5.7 Hz, 1H), 6.22 [s, 1H, H(12b)], 7.20–7.35 (m, 5H), 7.48 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.55 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR δ 14.4, 55.1, 83.3, 89.4, 123.7, 123.9, 125.7, 127.4, 127.9, 130.0, 132.3, 132.8, 136.5, 143.9, 173.1 (C=O).

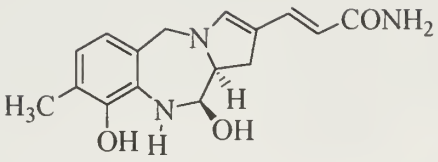
CHAPTER 4
SYNTHESES OF BENZODIAZEPINES, BENZOXAZEPINES AND BENZOTHIAZEPINES BY CYCLIZATIONS OF 1-HETEROARYLPROPYL-5-BENZOTRIAZOLYL-PYRROLIDIN-2-ONES AND 3-BENZOTRIAZOLYL-2-HETEROARYLPROPYL-1-ISOINDOLINONES

4.1 Introduction

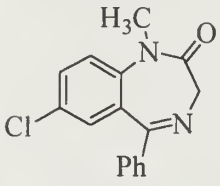
Fused ring systems which have a seven membered ring containing two heteroatoms e.g. benzodiazepines (N and N), benzoxazepines (N and O) and benzothiazepines (N and S) are of considerable interest. They possess varied biological activity. Some of them act on the central nervous system [86JMC1877] while others are useful hypolipidermic [86JPS622] and antiarrhytthmic [85P827] agents. Several natural products possess such skeletal frameworks. [87TL2473, 95TL6733, 75JACS2503] Benzodiazepines **4.1** are effective against Meniere's disease, [97US5817658] Anthramycin (**4.2**) has anti-cancer activity [97S75] and Diazepam (Valium, **4.3**) is used to treat anxiety disorders [85US4545935] (Figure 4.1).



4.1



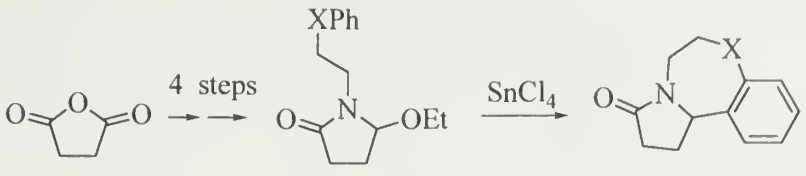
4.2
Anthramycin



4.3
Diazepam [Valium]

Figure 4.1

Several methods have been reported for the synthesis of 1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]benzoheteroazepin-3(2*H*)-ones [78CI347, 80AJC625, 83JOC2936]. Among them, the synthesis of benzodiazepines **4.6** from 1-(2-benzoheteroethyl)-5-ethoxy-2-pyrrolidinones (**4.5**) by Kraus and coworkers is the most noteworthy [83JOC2936] (Figure 4.2). However, the synthesis of intermediate **4.5** does require four steps from the dihydrofuran-2,5-dione (**4.4**).



4.4 **4.5**

4.6	X	Yield
a	NCH_3	70%
b	O	60%
c	S	26%

Figure 4.2

For the syntheses of 6,7-dihydroisoindolo[2,1-*d*][1,4]benzoheteroazepin-9(13b*H*)-ones **4.12** (X = NR`, O) a number of methods have been reported which include (Figure 4.3):

A. Condensation of 1,2-diamines **4.7** with 2-formylbenzoic acid (**4.8**) in PPA gave benzodiazepines **4.12** (X = NR') in 34–65% yields [72JOC3755].

B. Condensations of 2-aryloxyethylamines **4.9** with 2-formylbenzoic acid **4.8** yielded aminophthalides which were then cyclized to give benzo[*a*]1,4-oxazepino[5,4-*a*]isoindoles **4.12** (X = O) in yields of 18–70% [77BSCB1003, 78BSCB911].

C. Rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate (**4.10**) under Bischler-Napieralski conditions gave the benzoxazepines **4.12** (X = O) [94TL2751].

D. Scandium or copper triflate catalyzed acylaminoalkylation on α-methoxyisoindolones **4.11** afforded benzoxazepines **4.12** (X = O) in 61% yields [96S871].

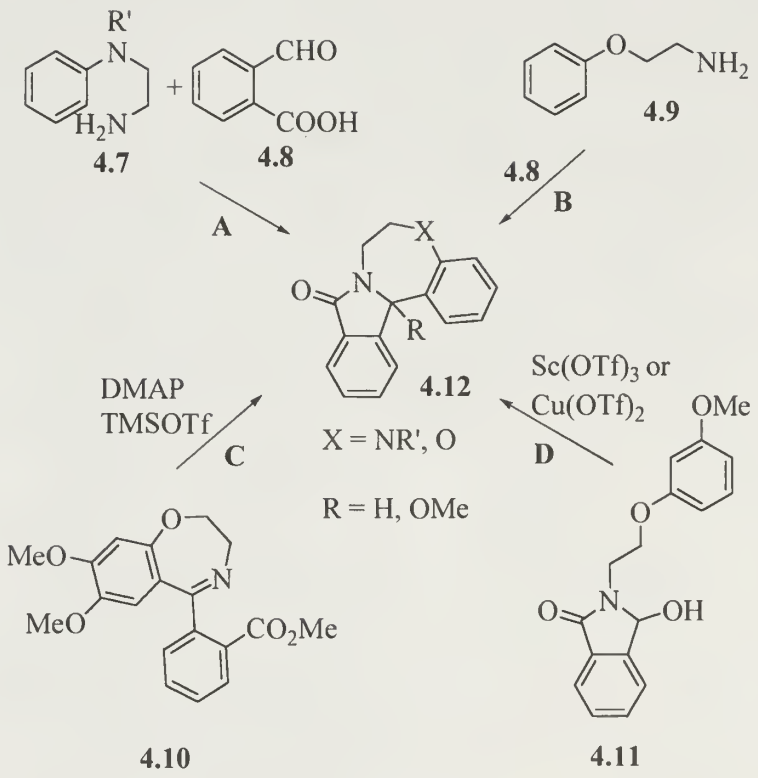


Figure 4.3

Although syntheses of such compounds have been accomplished, approaches featuring more versatile synthons would be advantageous. In addition, synthesis of optically active benzodiazepines has not been reported as yet. We report herein an interesting and efficient approach to the synthesis of benzodiazepines, benzoxazepines and benzothiazepines using our benzotriazole methodology.

4.2 Results and Discussion

Our initial approach was to mix as a one-pot reaction, 2,5-dimethoxy-2,5-dihydrofuran (**4.13**) benzotriazole, and *N*-(2-aminoethyl)-*N*-phenylamine (**4.14**) in

refluxing acetic acid in an attempt to obtain 1-(2-anilinoethyl)-5-(1*H*-1,2,3-benzotriazol-1-yl)-2-pyrrolidinone (**4.15**). It was planned to subscquently treat **4.15** with $TiCl_4$ to produce 1,2,5,6,7,11b-hexahydro-3*H*-pyrrolo[1,2-*d*][1,4]benzodiazepin-3-one (**4.16**). Unfortunately we did not get **4.16** but instead isolated 1-phenylhexahydro-5*H*-pyrrolo[1,2-*a*]imidazol-5-one (**4.17**) in 60% yield (Figure 4.4). We feel that due to the highly nucleophilic character of the lone electron pair on the secondary amine nitrogen of **4.14** as well as the excellent leaving-group properties of the benzotriazole function, **4.17** was probably formed via the intermediate **4.15**.

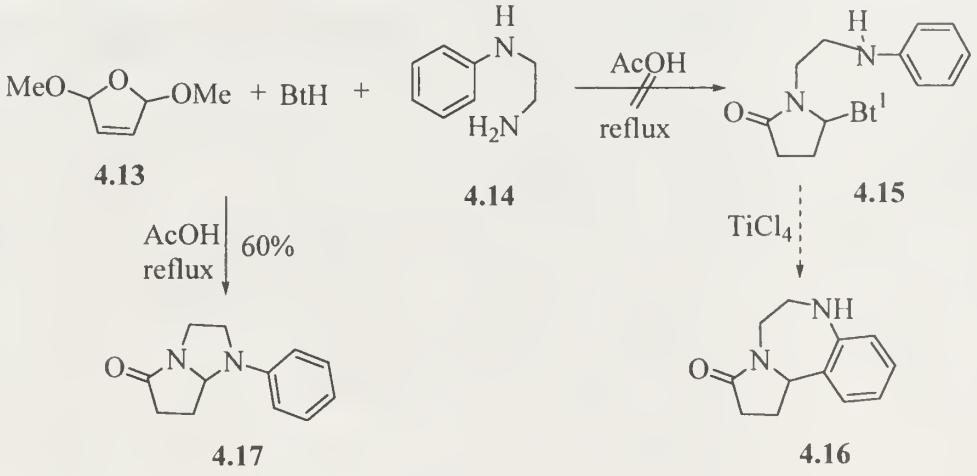
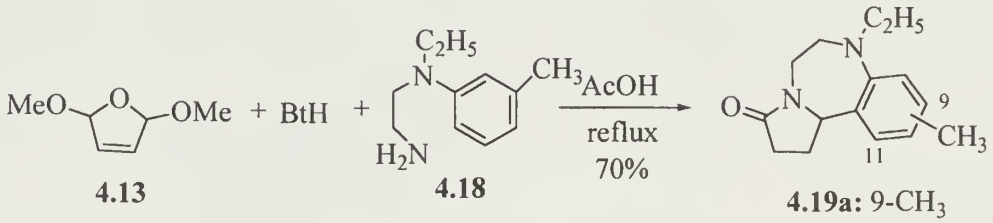


Figure 4.4

To circumvent the problem mentioned above, the cyclization reaction was done with *N*-(2-aminoethyl)-*N*-ethyl-*N*-(3-methylphenyl)amine (**4.18**) which contained a tertiary amine. The reaction of **4.18** with **4.13** and benzotriazole gave in a single step a 1:1 mixture of 7-ethyl-9-methyl-1,2,5,6,7,11b-hexahydro-3*H*-pyrrolo[1,2-*d*][1,4]benzo-diazepin-3-one (**4.19a**) and 7-ethyl-11-methyl-1,2,5,6,7,11b-hexahydro-3*H*-pyrrolo[1,2-

d][1,4]benzodiazepin-3-one (**4.19b**) in a total of 70% yield (Figure 4.5). However, the regio-isomers **4.19a** and **4.19b** could not be separated by column chromatography due to their close R_f values.



4.13 **4.18** **4.19a:** 9-CH_3

4.19b: 11-CH_3

Figure 4.5

A similar reaction of **4.18** with 2-formylbenzoic acid (**4.8**) and benzotriazole in refluxing toluene gave 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-[2-(ethyl-3-methylanilino)ethyl]-1-isoindolinone (**4.20a**) and 3-(2*H*-1,2,3-benzotriazol-2-yl)-2-[2-(ethyl-3-methylanilino)ethyl]-1-isoindolinone (**4.20b**) in 78% and 13% yield respectively. Overnight treatment of **4.20a** in refluxing acetic acid furnished a 1:1 mixture of 5-ethyl-3-methyl-5,6,7,13b-tetrahydro-9*H*-isoindolo[2,1-*d*][1,4]benzodiazepin-9-one (**4.21a**) and 5-ethyl-1-methyl-5,6,7,13b-tetrahydro-9*H*-isoindolo[2,1-*d*][1,4]benzodiazepin-9-one (**4.21b**) in 89% overall yield (Figure 4.6).

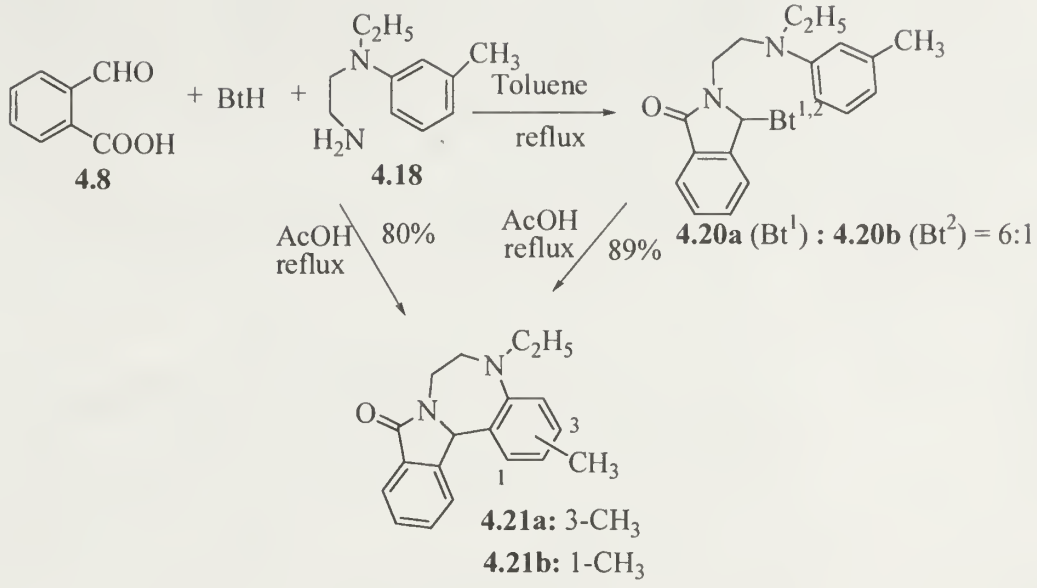


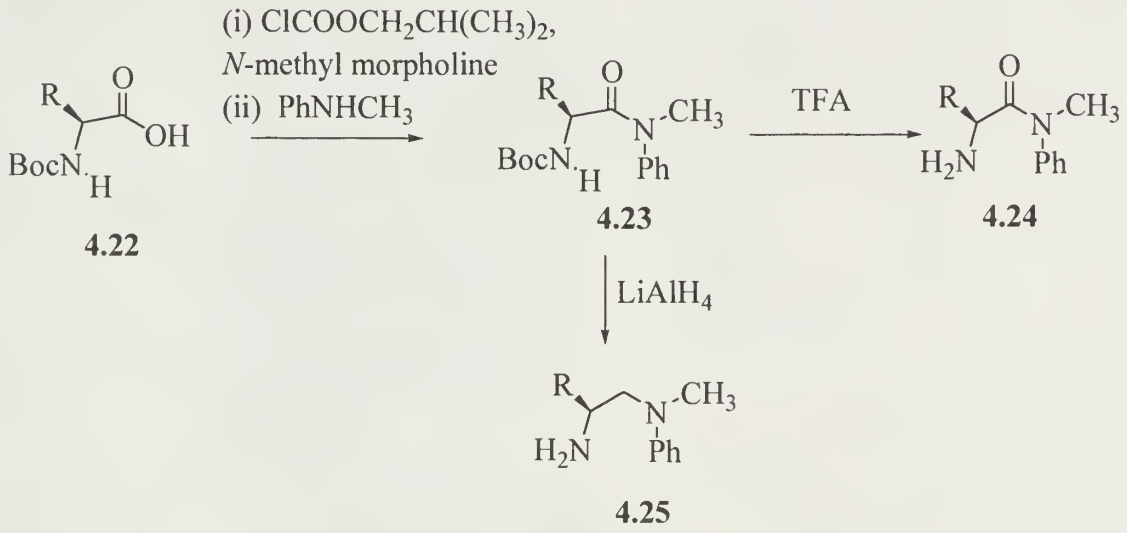
Figure 4.6

Interestingly, refluxing 2-formyl benzoic acid (**4.8**), benzotriazole and amine **4.18** in acetic acid directly gave a mixture of **4.21a** and **4.21b** in 80% yield. The above reaction gives us the possibility of making various benzodiazepines in a single step reaction from commercially available starting materials. It is obvious that the amine **4.18** is responsible for the formation of regio-isomers. Furthermore, few analogues of **4.18** are commercially available. Therefore, we prepared chiral precursors for benzodiazepines from commercially available *N*-Boc-α-amino acids **4.22**.

4.2.1 Synthesis of Chiral Precursors for Benzodiazepines from *N*-Boc-α-Amino Acids

N-Boc-α-amino acids **4.22** were condensed with *N*-methyl aniline to give *N*-Boc-α-amides **4.23** in 76–91% yields using the mixed anhydride method. [2000TL37]

Deprotection of the Boc group with HCl and dilute methanol gave the corresponding 2-amino-amides **4.24** in 80-85% yield. The Boc-protected amides **4.23** were reduced to the corresponding diamines **4.25** with $LiAlH_4$ in 70-80% yields (Figure 4.7).



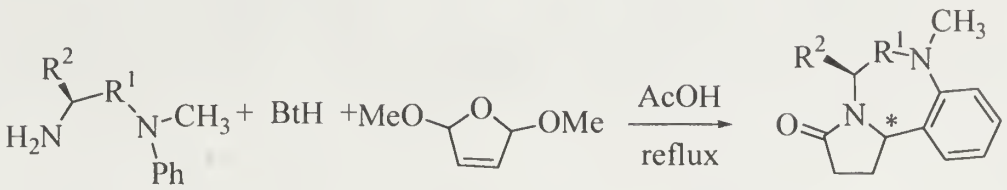
Entry	R	4. 23	4. 24	4.25
a	$CH(CH_3)_2$	91%	92%	85%
b	$CH_2CH(CH_3)_2$	80%	90%	80%
c	CH_2Ph	76%	90%	82%

Figure 4.7

4.2.2 Future work: Synthesis of Chiral Benzodiazepines

Having obtained the chiral 2-amino amides **4.24** and 1,2-diamines **4.25**, we then hope to reacted them with benzotriazole and 2,5-dimethoxy-2,5-dihydrofuran (**4.13**) in

refluxing acetic acid to obtain the corresponding 1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]benzohet-eroazepin-3(2*H*)-ones (**4.26**) (Figure 4.8).



4.24 (R^1 = C=O)

4.25 (R^1 = CH_2)

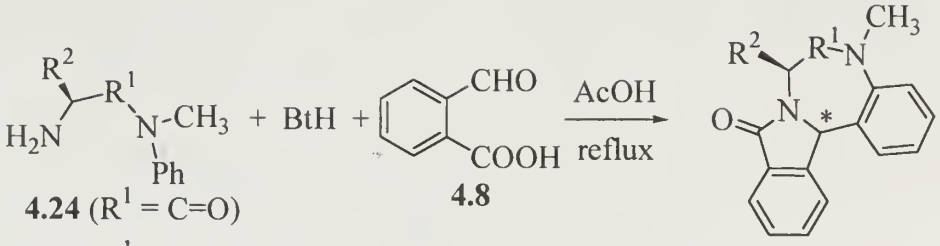
4.13

4.26

4.26	R^1	R^2
a	C=O	$CH(CH_3)_2$
b	C=O	$CH_2CH(CH_3)_2$
c	C=O	CH_2Ph
d	CH_2	$CH(CH_3)_2$
e	CH_2	$CH_2CH(CH_3)_2$
f	CH_2	CH_2Ph

Figure 4.8

In a similar manner reaction of chiral 2-amino amides **4.24** and 1,2-diamines **4.25** with benzotriazole and 2-formylbenzoic acid (**4.8**) in refluxing acetic acid would furnish the corresponding 6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones (**4.27**) (Figure 4.9).



4.24 (R^1 = C=O)

4.25 (R^1 = CH_2)

4.8

4.27

4.27	R^1	R^2
a	C=O	$CH(CH_3)_2$
b	C=O	$CH_2CH(CH_3)_2$
c	C=O	CH_2Ph
d	CH_2	$CH(CH_3)_2$
e	CH_2	$CH_2CH(CH_3)_2$
f	CH_2	CH_2Ph

Figure 4.9

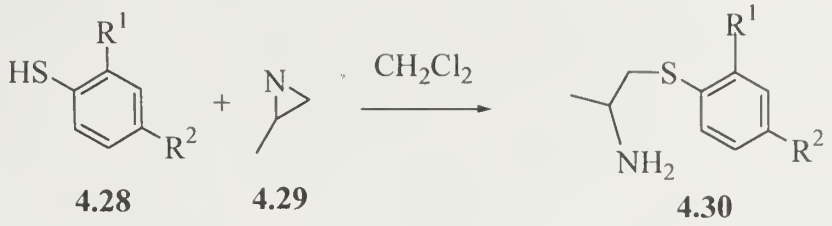
This work is currently under progress.

4.2.3 Synthesis of Precursors for Benzoxazepines and Benzothiazepines

We employed two methods for the synthesis of precursors for benzoxazepines and benzothiazepines (Figure 4.10). They are as follows

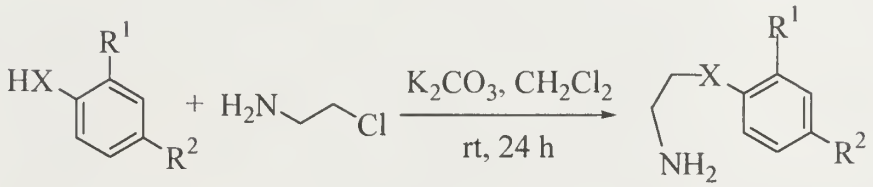
A. Treatment of substituted thiophenols **4.28** with 2-methylazirane (**4.29**) in CH_2Cl_2 at room temperature [51JACS2121] to give the corresponding substituted 2-(phenylsulfanyl)ethylamines **4.30** and

B. Treatment of phenols **4.31** or thiophenols **4.32** with 2-chloroethylamine hydrochloride in the presence of potassium carbonate to give 2-phenoxyethylamines **4.33** and 2-(phenylsulfanyl)ethylamines **4.34** respectively.



4.28 **4.29** **4.30**

4.30	R^1	R^2	Yield (%)
a	H	CH_3	80
b	CH_3	H	77
c	OCH_3	H	80



X = O **4.31**
S **4.32**

X = O **4. 33**
S **4. 34**

Compd	X	R^1	R^2	Yield (%)
4.33	O	H	H	75

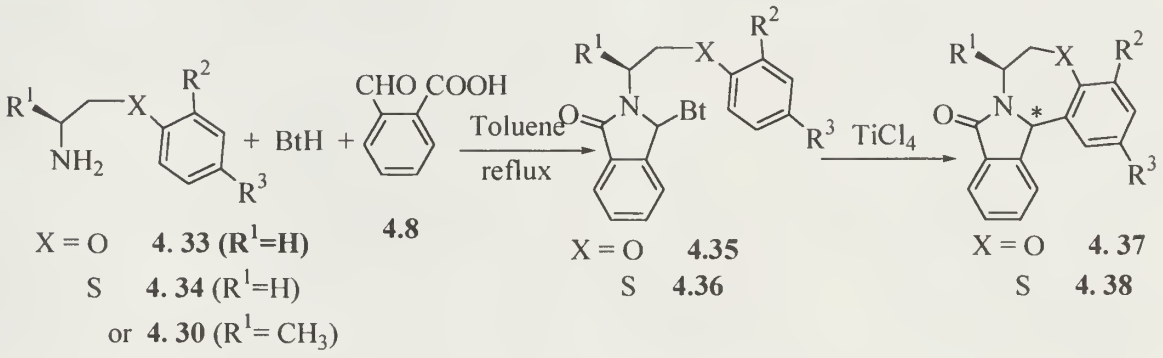
Figure 4.10

4.2.4 Synthesis of Benzoxazepines and Benzothiazepines

Having obtained 2-phenoxyethylamines **4.33** and 2-(phenylsulfanyl)ethylamines **4.34**, we then reacted them with benzotriazole and 2,5-dimethoxy-2,5-dihydrofuran (**4.13**) in refluxing acetic acid to try and obtain the corresponding 1,5,6,11b-

tetrahydropyrrolo[1,2-*d*][1,4]benzoheteroazepin-3(2*H*)-ones. However, only decomposition products were observed.

Reaction of 2-phenoxyethylamines **4.33** or 2-(phenylsulfanyl)ethylamines **4.34**, with benzotriazole and 2-formylbenzoic acid (**4.8**) in refluxing toluene furnished the corresponding 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(2-heteroarylethyl)-1-isoindolinones **4.35** or **4.36** in excellent yields. $TiCl_4$ was added to the crude mixture and the reaction refluxed for 24 to 48 hours to give 6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones **4.37** or **4.38** in 60–65% yields over the two steps (Figure 4.11).



	X	R^1	R^2	R^3	Yield (%)
4.37	O	H	H	H	60
4.38a	S	H	H	H	65
4.38b	S	CH_3	H	CH_3	-
4.38c	S	H	CH_3	H	65

Figure 4.11

Thus we have demonstrated that our benzotriazole methodology is a very versatile method for short chiral syntheses of benzodiazepines, benzoxazepines and benzothiazepines.

4.3 Experimental Section

THF was distilled from sodium-benzophenone prior to use. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini 300 NMR spectrometer (300 MHz and 75 MHz respectively) in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. HRMS were measured on an AEI-30 mass spectrometer. All of the reactions were carried out under N_2.

4.3.1 General Procedure for the Preparation of 3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(Ethyl-3-Methylanilino)Ethyl]-1-Isoindolinone (**4.20a**) and 3-(2*H*-1,2,3-Benzotriazol-2-yl)-2-[2-(Ethyl-3-Methylanilino)Ethyl]-1-Isoindolinone (**4.20b**)

2-Formylbenzoic acid (**4.8**) (6.00 g, 40 mmol), *N*-(2-aminoethyl)-*N*-ethyl-*N*-(3-methylphenyl)amine (**4.18**) (6.04 g, 40 mmol) and benzotriazole (7.14 g, 60 mmol) were dissolved in toluene and refluxed overnight with a Dean-Stark apparatus. The reaction was cooled after 24 hours and the toluene removed *in vacuo*.. 2M NaOH (20 mL) was added and it was extracted thrice with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and purified by column (Hexane/EtOAc: 5/1-3/1) to give **4.20a** and **4.20b**.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(ethyl-3-methylanilino)ethyl]-1-isoindolinone (**4.20a**). Yield, 78%; white microcrystals; mp 122 °C; ^{1}H NMR δ 1.04 (t, J = 7.2 Hz, 3H), 2.23 (s, 3H), 2.92–3.00 (m, 1H), 3.22 (m, 3H), 3.50–3.60 (m, 1H), 3.75–3.85 (m, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.40 (s, 3H), 7.00 (t, J = 8.1 Hz, 1H), 7.17 (t, J = 7.2 Hz, 1H), 7.27 (m, 2H), 7.39 (s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 8.05 (d, J =

8.1 Hz, 2H); ^{13}C NMR 11.9, 21.7, 38.0, 44.4, 47.5, 73.1, 109.2, 109.8, 112.7, 117.3, 120.4, 123.5, 124.0, 124.6, 128.1, 129.2, 130.5, 130.8, 131.8, 132.9, 139.0, 139.1, 146.9, 147.3, 167.3; Anal. Calcd. for $C_{25}H_{25}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 73.33, H, 6.40; N, 17.20.

3-(2*H*-1,2,3-Benzotriazol-2-yl)-2-[2-(ethyl-3-methylanilino)ethyl]-1-isoindolinone **(4.20b)**. Yield, 13%; white microcrystals; mp 118 °C; ^{1}H NMR δ 1.00 (t, J = 7.2 Hz, 3H), 2.22 (s, 3H), 2.92-3.00 (m, 1H), 3.22 (q, J = 7.0 Hz, 2H), 3.30–3.40 (m, 1H), 3.45–3.60 (m, 1H), 3.75–3.85 (m, 1H), 6.40 (s, 3H), 6.97 (t, J = 7.5 Hz, 1H), 7.14 (s, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.34–7.37 (m, 2H), 7.40–7.50 (m, 2H), 7.81–7.84 (m, 2H), 7.94 (d, J = 7.2 Hz, 1H); ^{13}C NMR 11.8, 21.6, 38.3, 44.4, 47.4, 78.0, 108.9, 112.3, 116.9, 118.2, 123.0, 123.6, 127.1, 128.9, 130.3, 131.4, 132.3, 138.6, 139.7, 144.6, 147.1, 167.6; Anal. Calcd for $C_{25}H_{25}N_5O$: C, 72.97; H, 6.12; N, 17.02. Found: C, 73.32, H, 6.36; N, 17.16.

4.3.2 General Procedure for the Preparation of Boc Amides **(4.23)**

To a cold solution of Boc protected amino acid (5.0 g, 20mmol) and N-methyl morpholine (2.02 g, 20mmol) in dry THF (50 mL) was added dropwise isobutyl chloroformate (2.72 g, 20mmol) in THF (10 mL) and stirred for half an hour. N-methyl aniline (2.14 g, 20mmol) was added dropwise and allowed to come to room temperature over a period of 2-3 hours. It was diluted with EtOAc (50 mL), washed with 10% Na_2CO_3 (2 x 30 mL), 1M HCl (15 mL) and brine (2 x 15 mL). It was dried over Na_2SO_4, evaporated and subjected to flash chromatography (30% EtOAc / hexanes) to give the Boc protected amides **4.23a-c** as clear oils.

Tert-Butyl *N*-(1*S*)-2-methyl-1-[(methylanilino)carbonyl]propylcarbamate **(4.23a)**. Yield 91%; white oil; ^{1}H NMR δ 0.82-0.85 (d, J = 6.6 Hz, 3H), 0.91-0.93 (d, J = 6.6 Hz, 3H), 1.55 (s, 9H), 1.89-1.95 (m, 1H), 3.41 (s, 3H), 4.33-4.38 (t, J = 8.7 Hz, 1H), 5.29-5.32 (d, J = 9 Hz, 1H), 7.35-7.60 (m, 5H); ^{13}C NMR 17.1, 19.4, 28.3, 31.4, 37.6, 55.5, 79.1, 127.4, 129.7, 142.8, 155.3, 172.4.

Tert-butyl N-{(1*S*)-3-methyl-1-[(methylanilino)carbonyl]butyl}carbamate **(4.23b)**. Yield 80%; clear oil; ^{1}H NMR δ 0.38-0.40 (d, J = 5.7 Hz, 3H), 0.71-0.73 (d, J = 6.3 Hz, 1H), 1.2 (m, 1H), 1.31-1.42 (m, 11H), 3.28 (s, 3H), 4.41 (m, 1H), 5.29-5.32 (d, J = 7.8 Hz, 1H), 7.30-7.47 (m, 5H); ^{13}C NMR 20.6, 23.2, 24.2, 28.3, 37.5, 42.4, 49.3, 79.1, 127.5, 128.0, 129.7, 142.7, 155.4, 173.2.

Tert-butyl N-{(1S)-1-benzyl-2-(methylanilino)-2-oxoethyl]carbamate **(4.23c)**. Yield 76%; clear oil; ^{1}H NMR δ 1.26 (m, 9H), 2.65-2.71 (m, 1H), 2.85-2.91 (m, 1H), 3.19 (s, 3H), 4.51-5.54 (m, J = 7.5 Hz, 1H), 5.28-5.30 (d, J = 8.4 Hz, 1H), 6.84-6.89 (m, 4H), 7.17-7.19 (m, 3H), 7.30-7.40 (m, 3H); ^{13}C NMR 28.1 37.3, 39.6, 52.1, 79.1, 126.4, 127.1, 127.8, 128.1, 129.2, 129.5, 136.4, 142.3, 154.6, 171.6.

4.3.3 General Procedure for the Preparation of Amides **(4.24)** by the Deprotection of Boc Amides **(4.23)**

To a cold solution of Boc Amides (5.14 g, 20mmol) and N-methyl morpholine (2.02 g, 20mmol) in dry THF (50 mL) was added dropwise isobutyl chloroformate (2.72 g, 20mmol) in THF (10 mL) and stirred for half an hour. N-methyl aniline (2.14 g, 20mmol) was added dropwise and allowed to come to room temperature over a period pf 2-3 hours. It was diluted with EtOAc (50 mL), washed with 10% Na_2CO_3 (2 x 30 mL),

1M HCl (15 mL) and brine (2 x 15 mL). It was dried over Na_2SO_4, evaporated and subjected to flash chromatography (30% EtOAc / hexanes) to give amides **4.24a-c** as clear oils.

(2*S*)-2-amino-N,3-dimethyl-N-phenylbutanamide **(4.24a)**. Yield 92%; clear oil; ^{1}H NMR δ 0.85-0.87 (d, J= 6.3 Hz, 6H), 1.88 (m, J=6.6Hz, 1H), 3.29 (s, 3H), 3.88 (d, J = 6.6 Hz, 2H), 7.35-7.15 (m, 5H); ^{13}C NMR 18.8, 27.7, 37.4, 71.6, 125.5, 125.6, 128.5, 143.2, 155.6.

(2*S*)-2-amino-N,4-dimethyl-N-phenylpentanamide **(4.24b)**. Yield 90%; clear oil; ^{1}H NMR δ 0.34 (d, J = 6.3 Hz, 3H), 0.68 (d, J = 6 Hz, 3H) , 1.23-1.37 (m, 1H), 1.45-1.68 (m, 2H), 3.27 (s, 3H), 4.04 (d, J = 6.3 Hz, 1H), 7.31-7.48 (m, 5H), 8.34 (bs, 2H); ^{13}C NMR 20.1, 22.7, 23.8, 38.0, 39.9, 49.7, 127.4, 128.8, 130.2, 141.5, 169.7.

(2*S*)-2-amino-N-methyl-N,3-diphenylpropanamide **(4.24c)**. Yield 90%; white oil; ^{1}H NMR δ 3.01-3.03 (m, 2H), 3.13 (s, 3H), 4.10-4.16 (t, J = 7.2 Hz, 1H), 6.60-6.90 (bs, 1H), 6.90-6.92 (m, 2H), 7.22-7.35 (m, 8H), 7.80-8.80 (m, 1H); ^{13}C NMR 37.4, 37.8, 52.1, 127.0, 127.6, 128.8, 129.3, 129.5, 130.0, 134.1, 141.3, 168.3.

4.3.4 General Procedure for the Preparation of 3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**4.35a**) and 3-(2*H*-1,2,3-Benzotriazol-2-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**4.35b**)

2-Formyl benzoic acid (**4.8**) (3.29 g, 22 mmol), 2-phenoxy-1-ethanamine (**4.33**) (3.0 g, 22 mmol) and benzotriazole (3.91 g, 33 mmol) were dissolved in toluene (20 mL) and refluxed overnight using a Dean Stark apparatus. The reaction was cooled after 24 h

and 2 M NaOH (20 mL) was added. It was extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and purified by column (Hexane/EtOAc: 5/1-1/1) to give **4.35a** and **4.35b.**

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**4.35a**). Yield 78%; m.p. 102-103°C; white microcrystals; ^{1}H NMR δ 3.20-3.296 (m, 1H), 3.58-3.76 (m, 2H), 4.06-4.15 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 7.20-7.30 (m, 2H), 7.32-7.39 (m, 1H), 7.40-7.55 (m, 3H), 7.60-7.75 (m, 3H), 7.85-8.00 (m, 2H), 8.05-8.15 (m, 2H); ^{13}C NMR 41.1, 41.9, 72.9, 109.7, 120.0, 123.5, 124.0, 124.8, 125.7, 128.3, 130.5, 130.9, 130.9, 133.3, 138.7, 146.4, 167.8; Anal. Calcd for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13.

3-(2*H*-1,2,3-Benzotriazol-2-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**4.35b**). yield 9%; white microcrystals; m.p. 110°C; Compound insufficient for characterization.

4.3.5 General Procedure for the Preparation of 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-[2-(arylsulfanyl)ethyl]-1-isoindolinone (**4.36a**) and 3-(2*H*-1,2,3-benzotriazol-2-yl)-2-[2-(arylsulfanyl)ethyl]-1-isoindolinone (**4.36b**)

2-Formylbenzoic acid (**4.8**) (2.65 g, 18 mmol), 2-(arylsulfanyl)-1-ethanamine **4.34** (2.7 g, 17.65 mmol) and benzotriazole (3.152 g, 26.47 mmol) were dissolved in toluene (20 mL) and refluxed overnight using a Dean Stark apparatus. The reaction mixture was cooled and 2 M NaOH (20 mL) was added. It was extracted thrice with CH_2Cl_2 and the organic phase was dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the residue was separated by column (Hexane/EtOAc: 5/1-1/1) to give **4.36a** and **4.36b**.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(phenylsulfanyl)ethyl]-1-isoindolinone (**4.36a**). Yield, 84%; white microcrystals; m.p. 100.3 °C; ^{1}H NMR δ 2.83–2.86 (m, 1H), 3.17–3.29 (m, 2H), 3.94–4.03 (m, 1H), 7.05–7.20 (m, 4H), 7.20–7.35 (m, 3H), 7.35–7.45

(m, 2H), 7.50–7.60 (m, 2H), 7.80–7.90 (m, 2H), 7.90–7.95 (m, 1H); ^{13}C NMR 30.9, 39.5, 72.6, 109.6, 120.0, 123.2, 123.7, 124.3, 126.0, 127.9, 128.6, 128.8, 130.2, 130.5, 131.2, 132.7, 134.2, 138.7, 146.6, 166.8. Anal. Calcd for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50. Found: C, 68.05, H, 4.72; N, 14.49.

3-(2*H*-1,2,3-Benzotriazol-2-yl)-2-[2-(phenylsulfanyl)ethyl]-1-isoindolinone (**4.36 b**). Yield, 11%; white microcrystals; m.p. 101.1°C; ^{1}H NMR δ 2.80–3.00 (m, 1H), 3.05–3.25 (m, 2H), 3.80–4.00 (m, 1H), 6.44 (d, J = 8.1 Hz, 1H), 7.00–7.35 (m, 5H), 7.40–7.65 (m, 2H), 8.00–8.06 (m, 2H); ^{13}C NMR 31.3, 40.2, 77.9, 118.4, 123.1, 124.0, 126.2, 127.3, 128.9, 129.3, 130.5, 132.6, 134.6, 139.9, 144.7, 167.7. Anal. Calcd for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50. Found: C, 68.25, H, 4.56; N, 14.50.

4.3.6 General Procedure for the Synthesis of 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13bH)-one (**4.37**)

To a solution of 3-(1H-1,2,3-benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**4.35a**) (250 mg, 0.675 mmol) in 20mL of toluene was added $TiCl_4$ (1.01 mL, 1.01 mmol) and refluxed for 48h. The black solution was cooled and quenched with 2 M NaOH, extracted thrice with CH_2Cl_2, dried over Na_2SO_4 and rotovapped. Column chromatography using 30% EtOAc/hexanes as an eluent gave **4.37** as an oil.

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-one (**4.37**). Yield, 60%; yellow oil; ^{1}H NMR δ 3.04–3.20 (m, 2H), 3.92–4.15 (m, 2H), 6.22 (s, 1H), 6.92 (dd, J = 7.5, 1.5 Hz, 1H), 7.15–7.30 (m, 2H), 7.47 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.61–7.67 (m, 2H), 7.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR 32.6, 42.6, 63.5, 124.1, 124.3, 127.4, 128.5, 128.7, 128.8, 131.5, 132.7, 134.0, 136.0, 139.1, 143.3, 168.7.

4.3.7 General Procedure for the Synthesis of 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones (**4.38a-c**)

To a solution of **4.36a-c** (250 mg, 0.65 mmol) in 20mL of toluene was added $TiCl_4$ (1.0 mL, 0.97 mmol) and refluxed for 48h. The black solution was cooled and quenched with 2M NaOH, extracted thrice with CH_2Cl_2, dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography using 30% EtOAc/hexanes as an eluent gave **4.38a-c**.

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (**4.38a**). Yield, 65%; yellow oil; ^{1}H NMR δ 2.95–3.20 (m, 2H), 3.88–4.15 (m, 2H), 6.21 (s, 1H), 6.91 (dd, J = 7.5, 1.5 Hz, 1H), 7.17–7.30 (m, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.61–7.67 (m, 2H), 7.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR 32.6, 42.6, 63.5, 124.1, 124.3, 127.4, 128.5, 128.6, 128.7, 131.4, 132.7, 134.0, 136.0, 139.1, 143.3, 168.7.

4-Methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (**4.38c**). Yield, 65%; yellow oil; ^{1}H NMR δ 2.54 (s, 3H), 2.85–3.03 (m, 1H), 3.13–3.20 (m, 1H), 3.93–3.98 (m, 2H), 6.31 (s, 1H), 6.73 (d, J = 7.8 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.62 (m, 1H), 7.93 (d, J = 7.2 Hz, 1H); ^{13}C NMR 21.9, 32.5, 42.1, 63.4, 124.0, 124.3, 125.2, 127.8, 128.5, 130.4, 131.4, 132.7, 135.7, 139.5, 141.3, 143.8, 168.6.

CHAPTER 5

SYNTHESES OF HETEROARYL BENZOTRIAZOLES BY MANNICH CONDENSATIONS

5.1 Introduction

1-Aryl benzotriazoles are useful synthons in thermal and photochemical Graebe-Ullmann reactions leading to carbazoles [1896LA16, 07CB378, 80JA1421, 85JCS(P1)2725], pyridoacridines [97JCS(P1)2739, 98JCS(P1)915], carbolines [93TL2673, 93JCS(P1)1261], benzocarbolines [94JMC3503], and fused tetraazapentalenes [86BSCB1107].

N-Arylbenzotriazoles have been synthesized by three pathways as reported in the literature.

A. Arylation of benzotriazole. Direct arylation of the benzotriazole anion succeeds with activated aryl halides [67T2863, 94S597], examples of which are shown in Figure 5.1.

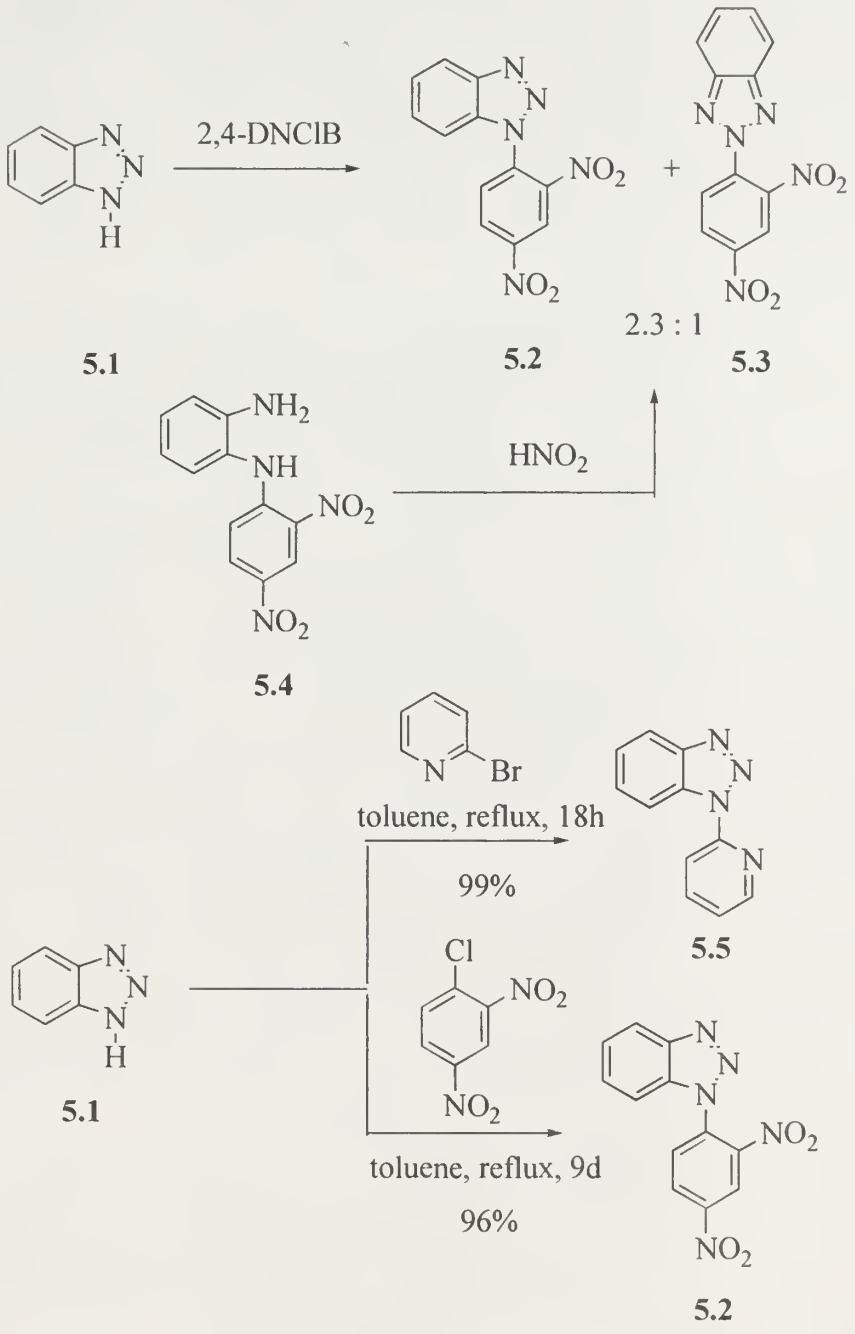
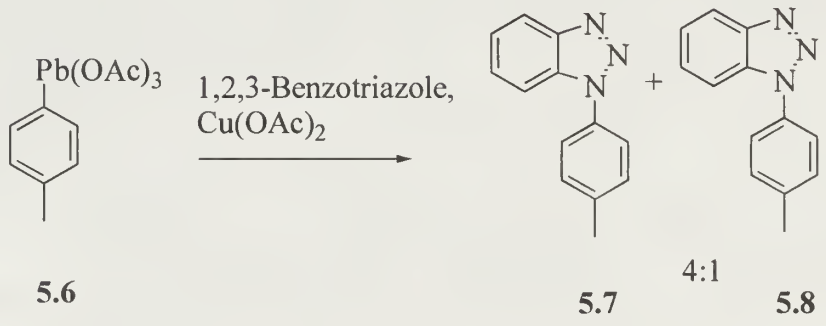
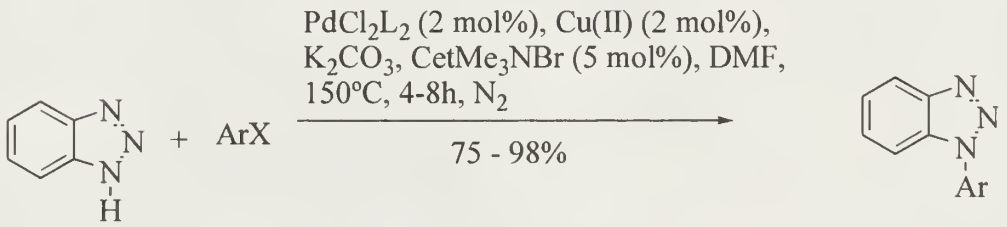

2,4-DNClB
NO2
NO2
+
NO2
NO2
2.3 : 1
5.1
5.2
5.3
NH2
NH
NO2
NO2
HNO2
5.4
Br
toluene, reflux, 18h
99%
5.5
Cl
NO2
NO2
5.1
toluene, reflux, 9d
96%
NO2
NO2
5.2

Figure 5.1

For the less reactive aryl halides, Cu-catalyzed reactions of benzotriazole (**5.1**) with $ArPb(OAc)_3$ [95JOC5678], or Pd-catalyzed reactions in the presence of a copper salt under

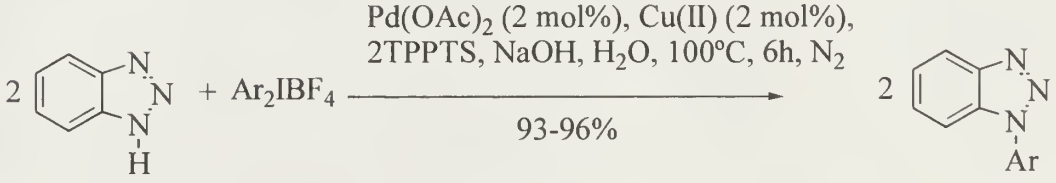


5.6 **5.7** **5.8**



5.1 ArX = PhI, *p*-FC_6H_4I, *p*-ClC_6H_4I, *p*-BrC_6H_4I, *p*-IC_6H_4I, *p*-MeC_6H_4I, *p*-$MeOC_6H_4I$, 2-$BrClC_5H_4N$ **5.9**

L = DPPM, DPPE, DPPP, DPPB, DPPF



5.1 **5.9**

Ar = Ph, *p*-MeC_6H_4,*p*-$MeOC_6H_4I$, *p*-ClC_6H_4

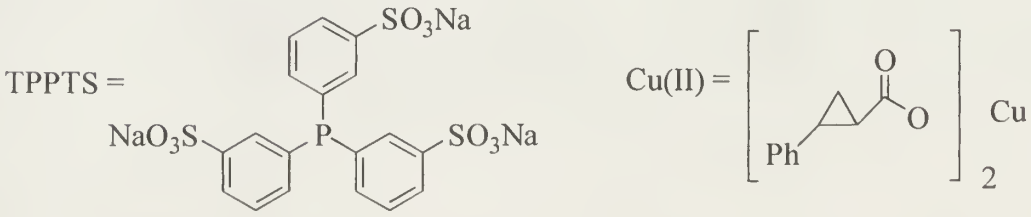


Figure 5.2

phase transfer conditions [98TL5617, 98TL 5621] need to be used as shown in Figure 5.2.

A. Construction of the benzotriazole ring from an aromatic substituent. This usually involves three steps, the arylation of an ortho-nitroaniline (**5.11**), reduction of the nitro-group and subsequent diazotization followed by cyclization [94JMC3503]. An alternative method is the reaction of aryl azides (**5.15**) with benzyne [87JCS(P1)403]. This is shown in Figure 5.3.

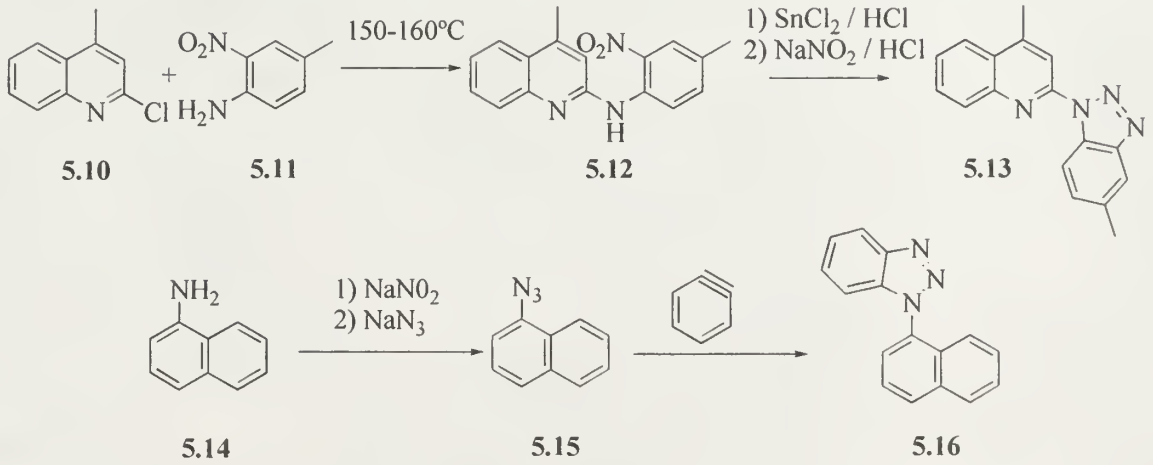


Figure 5.3

B. The direct synthesis of an aromatic system bearing a benzotriazole substituent. To our knowledge, the only such example to date is the one using 2-(benzotriazol-1-yl)vinamidinium salt (**5.18**) to prepare 5-(benzotriazol-1-yl)pyrimidines (**5.19**), 4-(benzotriazol-1-yl)pyrazoles (**5.20**) and 4-(benzotriazol-1-yl)pyrroles (**5.21**) [93T10205].

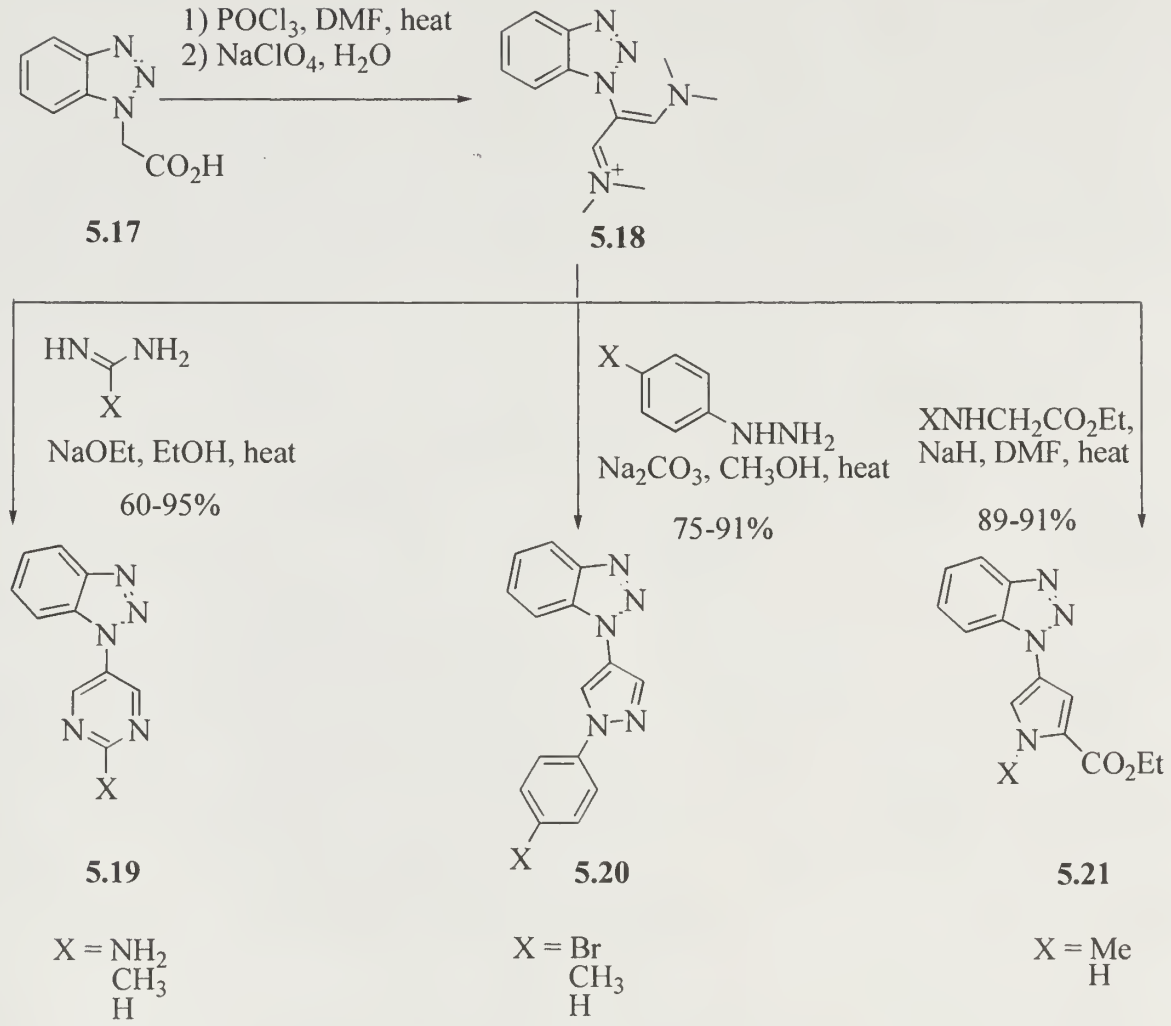


Figure 5.4

We now report a facile route to prepare N-(2-pyrryl)-benzotriazoles (**5.22**) and N-(1-isoindolyl)-benzotriazoles (**5.23**) via Mannich condensations of 2,5-dimethoxy-2,5-dihydrofuran (**5.24**) or α-phthalaldehyde (**5.25**) respectively with primary amines (**5.26**),in the presence of benzotriazole (**5.1**), as shown in Figure 5.5. Further, 2,5-dimethoxy-2,5-dihydrofuran (**5.24**) reacts with benzotriazole (**5.1**) to give N-(2-furyl)-benzotriazoles (**5.27**).

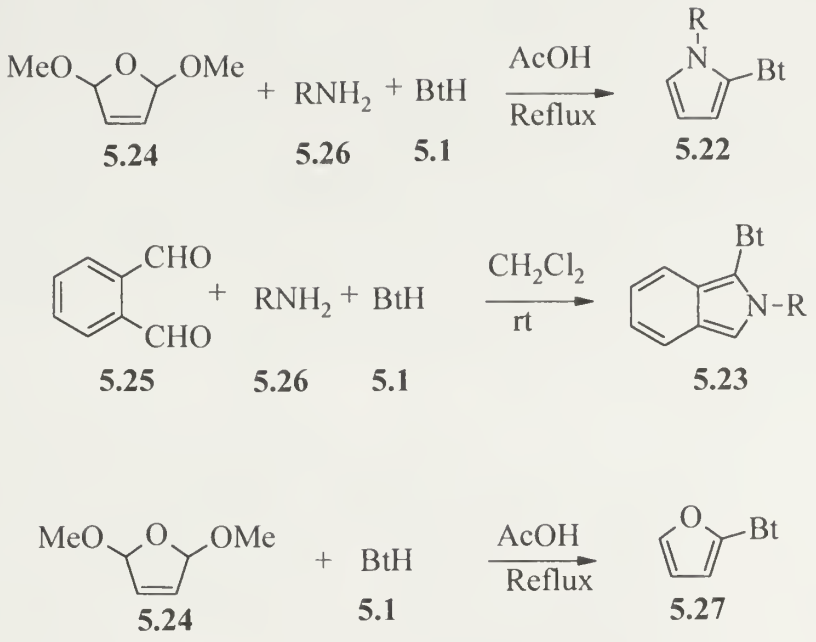


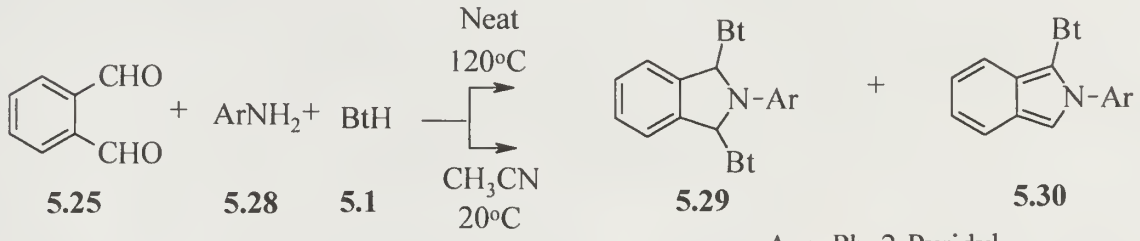
Figure 5.5

5.2 Results and Discussion

5.2.1 Preparation and Reactivity of *N*-substituted-2-(Benzotriazol-1-yl)isoindoles

Isoindoles (**5.23**) have attracted considerable theoretical and synthetic interest [88JOC2565, 72JCSCC397, 63JOC2464, 69JOC249, 75S252]. Previous work showed that the double Mannich condensation of α-phthalaldehyde (**5.25**) with primary aromatic amines (**5.28**) in the presence of 3 equivalents of benzotriazole (**5.1**) in acetonitrile [94H933] or at 120°C without solvent [87JCS(P1)799] gave exclusively or mainly the bis-benzotriazole-substituted isoindoline derivatives (**5.29**). Short reaction times (8 hr), gave 3% 2*H*-isoindole

(**5.30a**) with *p*-methylaniline, while no formation of 2*H*-isoindole (**5.30b**) was detected with *p*-methoxycarbonylaniline in CH_3CN at room temperature. However, 42% 2*H*-isoindole (**5.30a**) was formed by extending the reaction time to 336 hr (Figure 5.6) [94H933].



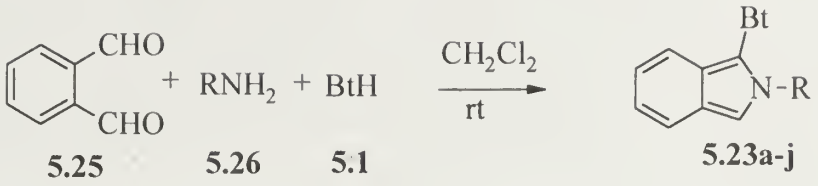
5.25 **5.28** **5.1** **5.29** **5.30**

Ar = Ph, 2-Pyridyl

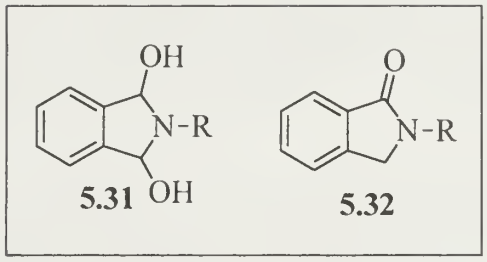
Ar	Reaction time (hr)	% Yield of Product **5.29**	**5.30**
a. (p-CH_3)Ph	8	83	3
	336	2	42
b. (p-CO_2CH_3)Ph	8	79	0

Figure 5.6

We now find, somewhat surprisingly, that using benzylamine (**5.26**, R = CH_2Ph) (instead of an aniline) in methylene chloride at room temperature gives exclusively the *N*-benzyl-2-(benzotriazol-1-yl)isoindole (**5.23a**) in 60% yield and none of the corresponding bis(benzotriazol-1-yl)isoindoline. Many other *N*-substituted-2-(benzotriazol-1-yl)isoindoles (**5.23b-5.23g**) were obtained in moderate to good yields (47-80%) under the same reaction conditions by using a variety of aliphatic primary amines, amino alcohols and amino acid esters (Figure 5.7).



5.25 **5.26** **5.1** **5.23a-j**



5.31 **5.32**

R = a. $PhCH_2$
b. $PhCH_2CH_2$
c. $CH_3(CH_2)_3$
d. $CH_3(CH_2)_2(CH_3)CH$
e. $CH_3(CH_2)_7$
f. 3-$PyCH_2$
g. (S)-$Ph(CH_3)CH$
h.(S)-$Ph(CH_2OH)CH$
i. (S)-$PhCH_2(CO_2CH_3)CH$
j. (S)-$CH_3(CO_2CH_3)CH$

Figure 5.7

In the absence of benzotriazole, primary amines are known to react with *o*-phthalaldehyde to produce the addition products (**5.31**), which undergo dehydration to the corresponding phthalimidines (**5.32**) in low yield [77JOC4217]. But, with the use of benzotriazole and β-mercaptoethanol as dual synthetic auxiliaries [96SL353] or with an intramolecular auxiliary, *e.g.* amino acid or amino alcohol [96SL781], phthalimide products (**5.32**) were obtained in good yield.

Under our reaction conditions, the amino alcohol, (2*S*)-2-phenyl-2-aminoethanol gave compound **5.23h** in good yield and its structure was confirmed by X-ray crystallography (Figure 5.8). Not shown in the diagram is the fact that the hydroxyl group is disordered over two positions, each of which involves hydrogen bonding to a nitrogen of a benzotriazole ring in an adjacent molecule.

The X-ray structure of **5.23h**

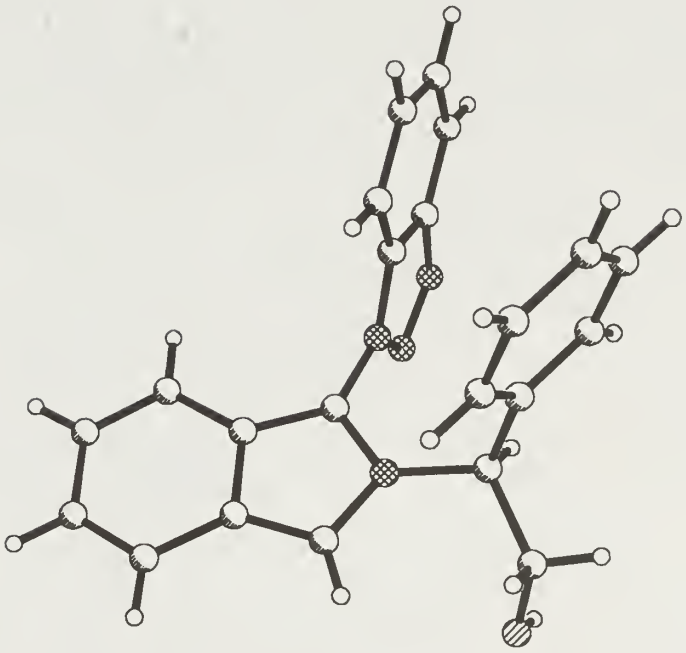


Figure 5.8

The 2-(benzotriazol-1-yl)isoindoles (**5.23**) are fairly stable at room temperature for several months. Heating **5.23g** in biphenyl ether to 250°C led to phenylimine (**5.33**) via a benzotriazole thermolysis, and **5.33** was further hydrolyzed to phthalimidine (**5.32a**). Interestingly, the thermolysis of **5.23h** in biphenyl ether under similar conditions gave the unusual benzotriazole migration products **5.36** (benzotriazol-1-yl) and **5.37** (benzotriazol-2-yl) in the ratio of 1:2 (presumably proceeding through intermediate **5.34**) along with a minor amount of the tricyclic lactam product (**5.35**) (Figure 5.9). The structure of **5.37** was unambiguously determined by X-ray crystallography. The crystals of **5.37** contain two independent molecules in the asymmetric unit, one of which is shown in Figure 5.10.

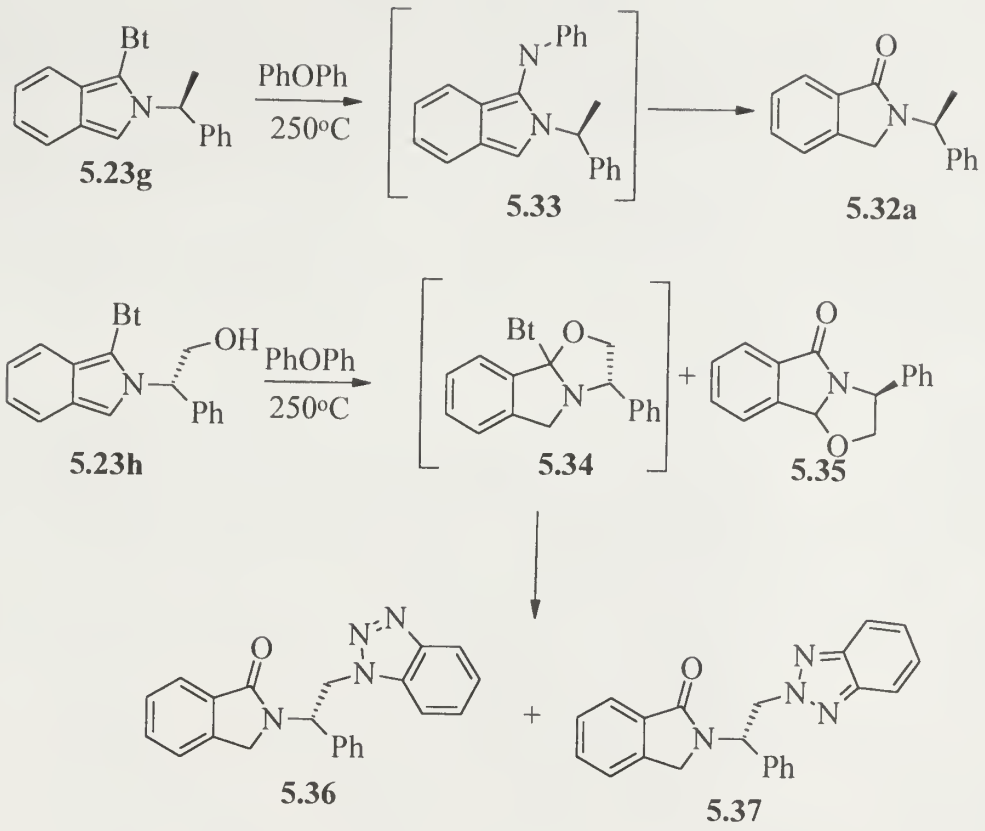


Figure 5.9

The X-ray structure of **5.37**

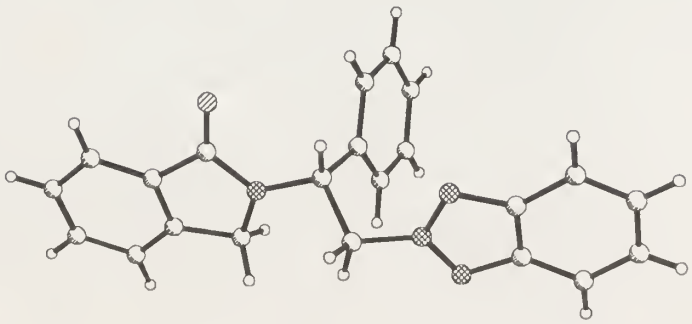


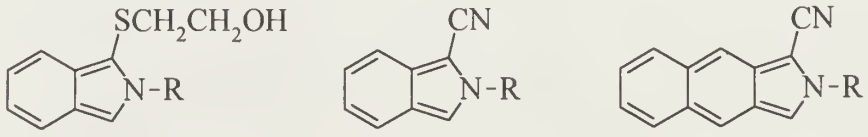
Figure 5.10

The reaction of the fluorogenic reagent *o*-phthalaldehyde (**5.25**) with a primary amine function and a nucleophile, β-mercaptoethanol, to produce a highly fluorescent *N*-substituted isoindole (**5.38**) has become a standard method for the very low-level analysis of amines and amino acids [71AC880, 76JA7098]. However, this method possesses a number of drawbacks:

A. Isoindole (**5.38**) is not very stable and decomposes to non-fluorescent products through autoxidation [84JOC4306].

B. Furthermore, some small peptides fail to give fluorescent products, thus limiting applications to simple amino acids [84AL1893].

N-Substituted-2-cyanoisoindoles (**5.39**, **5.40**) are much more stable and have a higher fluorescence efficiency [85CL1487, 86JOC3978], but the main drawbacks are the inconvenience of dealing with NaCN, and in addition for **5.40,** the commercial non-availability of 2,3-naphthalenedicarboxaldehyde, which is the starting material for **5.40** (Figure 5.11).



5.38 **5.39** **5.40**

Figure 5.11

We felt that *N*-substituted-2-(benzotriazol-1-yl)isoindoles (**5.23**) would be highly fluorescent and quite stable, and thus be good candidates for the analytical chemistry of primary amines. However to our disappointment we found that they were poorly fluorescent and the fluorescent emission was 10% of the expected value..

5.2.2 *N*-Substituted-2-(Benzotriazol-1-yl)pyrroles and 2-(Benzotriazol-1-yl)Furan

N-Substituted pyrroles are important intermediates with a wide variety of applications in fluorescence chemistry. They can be formed from primary amines by reaction with 2,5-dimethoxy-tetrahydrofuran or the reactive functional equivalent, 1,4-dichloro-1,4-dimethoxybutane [83JOC3059, 98JOC6715].

We now find that primary amines and benzotriazole can condense with 2,5-dimethoxy-2,5-dihydrofuran (**5.24**), a useful polyfunctionalized C_4 synthon [98TL5615], in acetic acid to give *N*-substituted-2-(benzotriazol-1-yl)pyrroles (**5.22**) in low yield (1.1% to 9.9%). The major products were those formed by rearrangement. No reaction occurred in refluxing toluene for 3 days with PTSA as catalyst. However, 2-(benzotriazol-1-yl)furan (**5.27**) was obtained in moderate yield (65%) by heating **5.24** with benzotriazole (**5.1**) in the absence of primary amines (Figure 5.12).

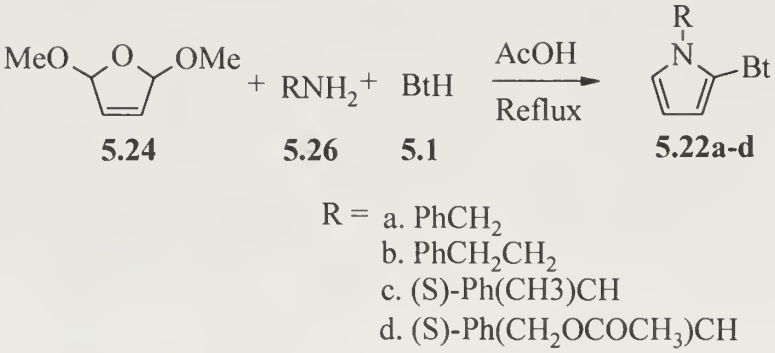


Figure 5.12

In summary, heteroaryl benzotriazole compounds, *N*-substituted-2-(benzotriazol-1-yl)isoindoles (**5.23a-j**), pyrroles (**5.22a-d**), and 2-(benzotriazol-1-yl)furan(**5.27**) were prepared in one step from *o*-phthalaldehyde (**5.25**) or 2,5-dimethoxy-2,5-dihydrofuran (**5.24**).

5.3 Experimental Section

Melting points were determined on a hot-stage apparatus without correction. Column chromatography was carried out on silica gel (230-400 mesh). The ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ solution (300 MHz and 75 MHz respectively), with TMS or $CDCl_3$ as internal references.

5.3.1 General Procedure for the Preparation of Compound **5.23**

A mixture of *o*-phthaldehyde (**5.25**) (1.34 g, 10 mmol), primary amine (**5.26**) (10 mmol) and benzotriazole (**5.1**) (2.38 g, 20 mmol) in CH_2Cl_2 (50 mL) was stirred with molecular sieves (4 A) at room temperature overnight. The reaction solution was filtrated from the molecular sieves, washed with 2 N NaOH (3 × 30 mL) and brine (3 × 30 mL). The organic phase was dried and concentrated to give a residue, which was purified by column chromatography (eluent: hexane/EtOAc) to afford compound **5.23**.

1-(2-Benzyl-2*H*-isoindole-1-yl)-1*H*-1,2,3-benzotriazole **(5.23a).** Yield: 56.5%; mp 154–155°C; ^{1}H NMR δ: 5.19 (d, J = 10.0 Hz, 2H), 6.82–6.83 (m, 2H), 6.94–7.06 (m, 7H), 7.28–7.36 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ: 51.7, 109.9, 111.4, 112.3, 116.6, 119.9, 120.0, 120.6, 121.6, 122.6, 123.2, 124.2, 127.0, 127.8, 128.2, 128.4, 135.1, 135.5, 145.0. Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.76; H, 4.97; N, 17.27. Found: C, 77.78; H, 4.93; N, 17.30. This compound was prepared by Mr. Long / Dr. Xilin Cui.

1-(2-Phenethyl-2*H*-isoindole-1-yl)-1*H*-1,2,3-benzotriazole **(5.23b).** Yield: 47.0%; ^{1}H NMR δ: 2.94–2.96 (m, 2H), 4.11–4.17 (m, 1H), 4.30–4.40 (m, 1H), 6.84–6.86 (m, 2H), 6.93–7.17 (m, 8H), 7.41–7.43 (m, 2H), 7.54 (d, J = 8.2 Hz, 1H), 8.17 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ: 37.9, 49.3, 110.2, 111.0, 111.7, 116.7, 120.0, 120.1, 121.4, 122.4, 122.9, 124.4, 126.6, 128.3, 128.4, 135.0, 137.1, 145.1. Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.08; H, 5.36; Found: C, 78.09; H, 5.53. This compound was prepared by Mr. Long / Dr. Xilin Cui.

1-(2-Butyl-2*H*-isoindole-1-yl)-1*H*-1,2,3-benzotriazole **(5.23c).** Yield: 52.0%; ^{1}H NMR δ: 0.73 (t, *J* = 7.4 Hz, 3H), 1.13–1.18 (m, 2H), 1.57–1.67 (m, 2H), 3.92–3.94 (m, 1H), 4.05–4.20 (m, 1H), 6.95–7.07 (m, 3H), 7.24–7.32 (m, 2H), 7.42–7.52 (m, 2H), 7.59 (d, *J* = 8.2 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ: 13.3, 19.6, 33.0, 47.5, 110.1, 111.0, 111.6, 116.6, 119.9, 120.2, 120.3, 121.4, 122.5, 122.9, 124.4, 128.5, 135.3, 145.1. Anal. Calcd for $C_{18}H_{18}N_4$: C, 74.46; H, 6.25; N, 19.29. Found: C, 74.31; H, 6.14; N, 19.07. This compound was prepared by Mr. Long / Dr. Xilin Cui.

1-[2-(1-Methylbutyl)-2*H*-isoindole-1-yl]-1*H*-1,2,3-benzotriazole **(5.23d).** Yield: 56.0%; (two isomers, the data of minor isomer are in brackets). ^{1}H NMR δ: 0.53 (t, *J* = 6.3 Hz, 2H), 0.81 (t, *J* = 6.2 Hz, 3H), 1.14–1.93 (m, 5H), 3.94–4.03 (m, 1H), 6.90–7.15 (m, 3H), 7.20–7.29 (m, 1H), 7.38–7.55 (m, 3H), 7.61 (d, *J* = 7.7 Hz, 1H), 8.18 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR δ: 13.3[13.6], 19.1[19.3], 22.8[22.9], 39.7[39.9], 52.7[52.8], 107.6[107.7], 109.9[110.1], 116.6[116.7], 119.8[119.9], 120.0[120.1], 120.3, 121.3[121.4], 122.7[122.8], 122.9, 124.3, 128.5, 135.5, 145.2. Anal. Calcd for $C_{19}H_{20}N_4$: C, 74.97; H, 6.62; N, 18.41. Found: C, 75.10; H, 7.12; N, 18.53. This compound was prepared by Mr. Long / Dr. Xilin Cui.

1-(2-Octyl-2*H*-isoindole-1-yl)-1*H*-1,2,3-benzotriazole **(5.23e).** Yield: 64.0%; ^{1}H NMR δ: 0.82 (t, *J* = 7.2 Hz, 3H), 1.07–1.29 (m, 10H), 1.61–1.80 (m, 2H), 3.92–3.94 (m, 1H), 4.10–4.12 (m, 1H), 6.94–7.07 (m, 3H), 7.27–7.31 (m, 2H), 7.42–7.51 (m, 2H), 7.59 (d, *J* = 9.1 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR δ: 13.9, 22.4, 26.3, 28.7, 28.8, 31.0, 31.5, 47.8, 110.1, 111.0, 111.5, 116.6, 119.9, 120.1, 120.2, 121.4, 122.5, 122.8, 124.4,

128.5, 135.2, 145.1. HRMS Calcd for $C_{22}H_{27}N_4$: 347.2235 (M+1). Found: 347.2235. This compound was prepared by Mr. Long / Dr. Xilin Cui.

1-[2-(3-Pyridinylmethyl)-2*H*-isoindole-1-yl]-1*H*-1,2,3-benzotriazole **(5.23f).** Yield: 53.0%; ^{1}H NMR δ: 5.22–5.28 (m, 2H), 6.94–7.07 (m, 5H), 7.15 (d, *J* = 6.9 Hz, 1H), 7.30–7.40 (m, 3H), 7.59 (d, *J* = 7.8 Hz, 1H), 8.10–8.16 (m, 2H), 8.30 (d, *J* = 4.5 Hz, 1H); ^{13}C NMR δ: 49.1, 109.7, 111.3, 112.2, 116.5, 120.0, 120.4, 121.9, 122.7, 123.2, 123.4, 124.4, 128.5, 131.3, 134.6, 134.8, 144.9, 148.2, 149.2. Anal. Calcd for $C_{20}H_{15}N_5$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.83; H, 5.01; N, 21.70.

1-{2-[(1*S*)-1-Phenylethyl]-2*H*-isoindole-1-yl}-1*H*-1,2,3-benzotriazole **(5.23g).** Yield: 80.0%; (Two isomers, the data of minor isomer are in brackets). ^{1}H NMR δ: 1.96 (d, *J* = 6.9 Hz, 3H) [1.76 (d, *J* = 6.9 Hz, 3H)], 5.54 (q, *J* = 6.9 Hz, 1H) [5.36 (q, *J* = 6.9 Hz, 1H)], 6.64–7.68 (m, 13H), 8.06 (d, *J* = 8.1 Hz, 1H) [8.18 (d, *J* = 8.1 Hz, 1H)]; ^{13}C NMR δ: 22.0[21.6], 56.4[55.7], 108.9, 110.0, 116.6[116.8], 119.7, 1203., 121.5[121.6], 123.1[123.2], 124.0, 125.2, 126.7, 127.5, 128.0, 128.4, 128.5[128.6], 135.5, 141.4, 145.0. Anal. Calcd for $C_{22}H_{18}N_4$: C, 78.07; H, 5.37; N, 16.56. Found: C, 77.83; H, 5.42; N, 16.62.

(2*S*)-2-[1-(1*H*-1,2,3-Benzotriazol-1-yl)-2*H*-isoindole-2-yl]-2-phenyl-1-ethanol **(5.23h).** (Two isomers, the data of minor isomer are in brackets). Yield: 61.0%; mp 187–188°C; ^{1}H NMR δ: 2.50–2.60 (m, 1H) [2.20–2.30 (m, 1H)], 4.30–4.40 (m, 2H) [4.15–4.25 (m, 2H)], 5.45–5.50 (m, 1H) [5.30–5.40 (m, 1H)], 6.70–6.85 (m, 2H), 6.90–7.10 (m, 5H), 7.20–7.80 (m, 6H), 8.00–8.10 (m, 1H); ^{13}C NMR δ: 62.7[62.2], 63.0, 109.7, 110.6[110.5], 111.2[111.0], 115.9[116.2], 119.7[119.4], 120.3[120.0], 120.7[120.4], 121.1[121.0], 122.3[121.8], 122.9[123.2], 124.3[124.6], 126.1[127.1], 128.0[127.6], 128.2,

128.5[128.4], 135.6[134.8], 137.8[137.7], 144.6[144.3]. Anal. Calcd for $C_{22}H_{18}N_4O$: C, 74.56; H, 5.12; N, 15.81. Found: C, 74.54; H, 5.06; N, 15.90.

Methyl-2(*S*)-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2*H*-isoindole-2-yl]-3-phenyl propanoate **(5.23i).** (Two isomers, the data of minor isomer are in brackets). Yield: 72.4%; ^{1}H NMR δ: 3.36–3.45 (m, 3H), 3.60–3.70 (m, 2H), 4.90–5.00 (m, 1H), 6.50–6.64 (m, 1H), 6.85–7.01 (m, 5H), 7.18–7.44 (m, 5H), 7.56–7.63 (m, 2H), 8.10–8.16 (m, 1H); ^{13}C NMR δ: 41.2[40.5], 54.7[54.2], 62.4[61.5], 112.0, 118.5, 121.5[121.2], 122.0[121.9], 123.6, 124.6, 125.0[125.1], 126.0[126.2], 128.7[128.9], 129.8, 130.0, 130.2, 130.7, 136.9[136.8], 146.7, 171.1. Anal. Calcd for $C_{24}H_{20}N_4O_2$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.68; H, 5.10; N, 13.81.

Methyl-2(*S*)-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2*H*-isoindole-2-yl]-propanoate **(5.23j).** (Two isomers, the data of minor isomer are in brackets). Yield: 43.0%; ^{1}H NMR δ: 1.88 (d, J = 5.1 Hz, 3H) [1.77 (d, J = 5.1 Hz, 3H)], 3.39 (s, 3H) [3.70 (s, 3H)], 4.90–5.05 (m, 1H) [4.70–4.80 (m, 1H)], 6.97–7.10 (m, 3H), 7.25–7.30 (m, 1H), 7.43–7.58 (m, 3H), 7.62–7.76 (m, 1H), 7.93–8.20 (m, 1H); ^{13}C NMR δ: 17.8, 52.5, 53.9, 109.3, 110.0, 110.4, 116.6, 120.2, 121.8, 122.8, 123.5, 124.5, 128.5, 130.9, 133.6, 135.3, 145.1, 170.1. HRMS Calcd for $C_{18}H_{17}N_4O_2$ 321.1352 (M^++1) Found: 321.1352 (M^++1). This compound was prepared by Mr. Long / Dr. Xilin Cui.

5.3.2 General Procedure for the Thermolysis of Compounds **5.23g** and **5.23h**

Compound **5.23g** (or **5.23h**) (0.2 g) was mixed with biphenyl ether (10 g) and the mixture was heated at reflux temperature (250°C) until TLC analysis showed that all the starting material had been consumed (approximately 2 hr). The reaction mixture was added to the top of a silica gel column and the column eluted with hexane to remove biphenyl ether. The product was then eluted with hexane/EtOAc.

2-[(1*S*)-1-Phenylethyl]-1-isoindolinone **(5.32a)** [97TL8265]. From **5.23g**, yield: 70.0%; ^{1}H NMR δ: 1.70 (d, *J* = 7.2 Hz, 3H), 3.99 (d, *J* = 17.1 Hz, 1H), 4.33 (d, *J* = 17.1 Hz, 1H), 5.82 (q, *J* = 7.2 Hz, 1H), 7.26–7.36 (m, 6H), 7.42–7.52 (m, 2H), 7.88 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR δ: 17.3, 45.6, 49.1, 122.7, 123.8, 127.1, 127.5, 128.0, 128.6, 131.1, 132.9, 140.6, 141.3, 168.0. MS (EI): 237 (M, 70), 222 (100), 160 (30), 119 (40).

(3*S*)-3-Phenyl-2,3-dihydro[1,3]oxazolo[2,3-a]isoindol-5(9b*H*)-one (**5.35**).

[97TL3627] From **5.23h**, yield: 10.0%; ^{1}H NMR δ: 4.17 (t, *J* = 8.1 Hz, 1H), 4.84 (t, *J* = 8.1 Hz, 1H), 5.23 (t, *J* = 7.5 Hz, 1H), 6.06 (s, 1H), 7.30–7.51 (m, 5H), 7.56–7.66 (m, 2H), 7.74–7.86 (m, 2H); ^{13}C NMR δ: 58.0, 78.0, 91.8, 124.0, 124.5, 126.0, 127.6, 128.8, 130.7, 132.9, 139.6, 142.0, 153.4, 174.0. MS (EI): 251 (M, 5), 221 (100), 193 (30), 165 (15). This compound was prepared by Mr. Long / Dr. Xilin Cui.

2-[(1*S*)-2-(2*H*-1,2,3-Benzotriazol-1-yl)-1-phenylethyl]-1-isoindolinone **(5.36).** From **5.23h**, yield: 20.0%; ^{1}H NMR δ: 4.10 (d, *J* = 16.8 Hz, 1H), 4.61 (d, *J* = 16.8 Hz, 1H), 5.29 (dd, *J* = 6.3 Hz, 14.1 Hz, 1H), 5.65 (dd, *J* = 9.3 Hz, 14.1 Hz, 1H), 6.03 (dd, *J* = 6.6 Hz, 9.0 Hz, 1H), 7.20–7.68 (m, 10H), 7.73 (t, *J* = 7.8 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR

δ: 47.8, 48.6, 55.5, 109.5, 119.9, 122.8, 123.7, 124.0, 127.7, 127.8, 128.0, 128.7, 129.1, 131.6, 132.0, 133.1, 136.2, 141.2, 145.8, 168.9. Anal. Calcd for $C_{22}H_{18}N_4O$: C, 74.55; H, 5.13; N, 15.81. Found: C, 74.26; H, 4.95; N, 15.56. This compound was prepared by Mr. Long / Dr. Xilin Cui.

2-[(1*S*)-2-(2*H*-1,2,3-Benzotriazol-2-yl)-1-phenylethyl]-1-isoindolinone (**5.37**). From **5.23h**, yield: 40.0%; ^{1}H NMR δ: 4.20 (d, *J* = 16.2 Hz, 1H), 4.71 (d, *J* = 16.2 Hz, 1H), 5.38 (dd, *J* = 5.4 Hz, 15.0 Hz, 1H), 5.60 (dd, *J* = 10.5 Hz, 13.2 Hz, 1H), 6.34 (dd, *J* = 5.1 Hz, 10.8 Hz, 1H), 7.30–7.41 (m, 7H), 7.46–7.51 (m, 3H), 7.70–7.78 (m, 3H); ^{13}C NMR δ: 46.9, 55.5, 56.3, 118.1, 122.8, 123.9, 126.4, 127.5, 127.9, 128.6, 129.1, 131.4, 132.2, 136.5, 141.2, 144.5, 168.5. Anal. Calcd for $C_{22}H_{18}N_4O$: C, 74.55; H, 5.13; N, 15.81. Found: C, 74.63; H, 5.02; N, 15.63. This compound was prepared by Mr. Long / Dr. Xilin Cui.

5.3.3 General Procedure for the Preparation of Compounds **5.22a-d**

2,5-Dimethoxy-2,5-dihydrofuran (**5.24**) (1.3 mL, 10 mmol), primary amine (**5.26**) (10 mmol) and benzotriazole (**5.1**) (2.6 g, 22 mmol) were added to 25 mL acetic acid and refluxed for 24 hr. The reaction vessel was cooled, CH_2Cl_2 (50 mL) added and then washed with 2 N NaOH (3 × 30 mL). The organic layer was dried over Na_2SO_4, and evaporation of the solvent gave a crude mixture. The crude product was further purified by column chromatography with hexanc/EtOAc as eluent.

1-(1-Benzyl-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**5.22a**). Yield: 3.0%; ^{1}H NMR δ: 5.14 (s, 2H), 6.59–6.60 (m, 1H), 6.80–6.81 (m, 1H), 7.15–7.16 (m, 1H), 7.21-7.25 (m,

2H), 7.32–7.39 (m, 3H), 7.48 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 8.08 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ: 54.1, 103.6, 110.4, 114.2, 119.9, 121.3, 122.2, 123.9, 127.3, 127.5, 128.1, 128.9, 132.7, 136.8, 145.8. Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.42; H, 5.15. Found: C, 74.21; H, 5.24.

1-(1-Phenethyl-1*H*-pyrrol-2-yl)-1*H*-1,2,3-benzotriazole (**5.22b**). Yield: 1.1%; ^{1}H NMR δ: 3.10 (t, J = 6.8 Hz, 2H), 4.17 (t, J = 6.8 Hz, 2H), 6.55–6.60 (m, 1H), 6.65–6.70 (m, 1H), 6.98–6.99 (m, 1H), 7.10–7.15 (m, 2H), 7.20–7.39 (m, 4H), 7.48 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 7.2 Hz, 1H), 8.07 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ: 38.1, 51.8, 103.3, 110.4, 113.7, 119.7, 120.7, 121.6, 123.8, 126.8, 127.4, 128.6, 132.7, 137.8, 145.7. MS (EI): 288 (M, 10), 260 (10), 169 (100). HRMS Calcd for $C_{18}H_{16}N_4$: 289.1453 (M^+) Found: 289.1451.

1-{1-[(1*S*)-1-Phenylethyl]-1*H*-pyrrol-2-yl}-1*H*-1,2,3-benzotriazole (**5.22c**). Yield: 2.1%; ^{1}H NMR δ: 1.90 (d, J = 7.2 Hz, 3H), 5.32 (q, J = 7.2 Hz, 1H), 6.56–6.58 (m, 1H), 6.83–6.85 (m, 1H), 7.17–7.20 (m, 3H), 7.27–7.37 (m, 4H), 7.46 (t, J = 7.5 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H); ^{13}C NMR δ: 21.9, 58.9, 103.2, 110.5, 112.8, 119.7, 119.8, 119.9, 123.9, 125.9, 127.5, 127.9, 128.8, 132.7, 142.2, 145.8. HRMS Calcd for $C_{18}H_{16}N_4$: 289.1453 (M^+) Found: 289.1451.

(2*S*)-2-[2-(1*H*-1,2,3-Benzotriazol-1-yl)-1*H*-pyrrol-1-yl]-2-phenylethyl acetate (**5.22d**). Yield: 9.9%; ^{1}H NMR δ: 2.07 (s, 3H), 4.72–4.78 (m, 2H), 5.50–5.51 (m, 1H), 6.63–6.64 (m, 1H), 6.89–6.92 (m, 1H), 7.25–7.27 (m, 3H), 7.36–7.40 (m, 4H), 7.51 (t, J = 8.1 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ: 20.8, 62.3, 65.1, 103.7, 110.4, 111.1, 113.3, 120.0, 120.4, 123.9, 126.7, 127.6, 128.8, 129.1, 136.8, 170.5. HRMS Calcd for $C_{20}H_{18}N_4O_2$: 347.1508 (M^+) Found: 347.1525.

1-(2-Furyl)-1H-1,2,3-benzotriazole (**5.27**). 2,5-Dimethoxy-2,5-dihydrofuran (**5.24**) (1.3 mL, 10 mmol) and benzotriazole (**5.1**) (2.6 g, 22 mmol) were added to 25 mL acetic acid and refluxed for 24 hr. The reaction vessel was cooled, CH_2Cl_2 (50 mL) added and the product washed with 2 N NaOH (3 × 30 mL). The organic layer was dried over Na_2SO_4, the solvent evaporated to give a crude mixture, which was further purified on a column with hexane/EtOAc as eluent to give **5.27** in 67.0% yield. ^{1}H NMR δ: 6.63 (d, J = 1.5 Hz, 1H), 6.69 (d, J = 3.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.50 (br s, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ: 100.5, 110.6, 111.8, 120.1, 124.7, 128.8, 129.7, 132.2, 140.4, 145.4. Anal. Calcd for $C_{10}H_7N_3$: C, 64.85; H, 3.82. Found: C, 65.09; H, 3.83.

5.3.4 X-Ray Crystallography

Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized Mo Kα radiation (λ = 0.7107 °A). The structures were solved by direct methods and refined on F^2 using all data by full-matrix least-squares procedures. Hydrogen atoms were included in calculated positions except for the OH hydrogens, which were located from a difference map.

Crystal Data for **5.23h** at 23 °C: $C_{22}H_{18}N_4O$, M = 354.4, orthorhombic, space group $P2_12_12_1$; a = 9.685(1), b = 10.709(1), c = 17.169(2); V = 1780.8(2), Z = 4, F(000) = 744, D_x = 1.322 g cm^{-3}; colorless block, 0.62 x 0.52 x 0.26 mm;? μ = 0.08 mm^{-1}, $2\theta_{max}$ 54°; 3196

unique reflections, 255 parameters, wR = 0.1107 for all data, R = 0.0475 for 2203 data with $I > 2\sigma$? (I).

Crystal Data for **5.37** at -115°C: $C_{22}H_{18}N_4O$, M = 354.4, triclinic, space group $P1$; a = 6.410(1), b = 10.612(2), c = 13.621(3) A, α = 102.995(4), β = 93.814, γ = 99.126(4) °; V = 886.3(1), Z = 2, F(000) = 372, D_x = 1.328 g cm^{-3}; colorless block, 0.71 x 0.58 x 0.20 mm; μ = 0.08 mm^{-1}, $2\theta_{max}$ 53°; 5818 unique reflections, 487 parameters, wR = 0.1175 for all data, R = 0.0469 for 4917 data with $I > 2\sigma$ (I).

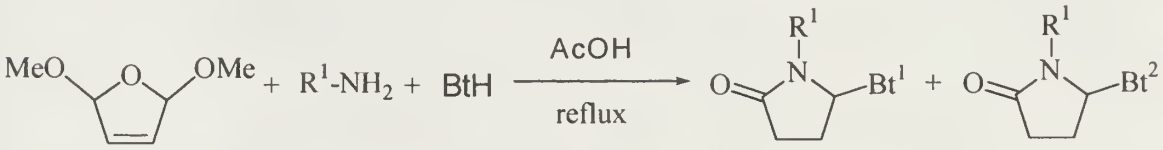
The X-ray crystallography was done by Professor Peter J. Steel, Department of Chemistry, University of Canterbury, Christchurch, New Zealand

CHAPTER 6
SUMMARY, CONCLUSIONS AND FUTURE WORK

6.1 Summary

Using some of the versatile properties of the synthetic auxiliary benzotriazole, the synthesis and utility of several types of benzotriazole-containing intermediates has been explored. These have then been used to make a variety of heterocyclic compounds.

In Chapter 2 we synthesized 5-benzotriazole substituted pyrrolidin-2-ones **6.3** from 2,5-dimethoxy-2,5-dihydrofuran (**6.1**), primary amines **6.2** and benzotriazole (Figure 6.1).

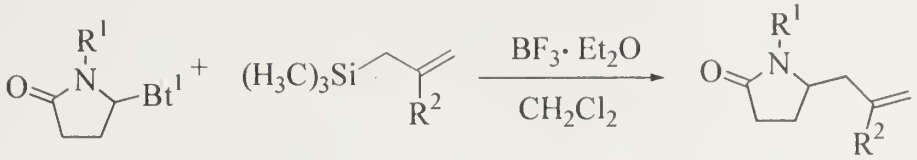


6.1 **6.2** **6.3**

Figure 6.1

These 5-benzotriazole substituted pyrrolidin-2-ones **6.3** were reacted with

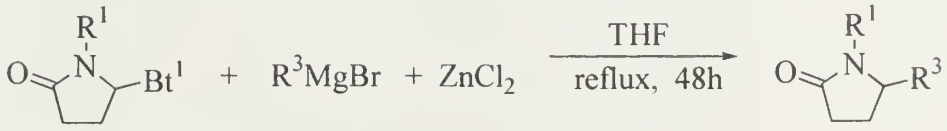
1. Allylsilanes and $BF_3.Et_2O$ to give 5-allyl-substituted pyrrolidin-2-ones **6.4** in good to excellent yields (Figure 6.2).



6.3 **6.4**

Figure 6.2

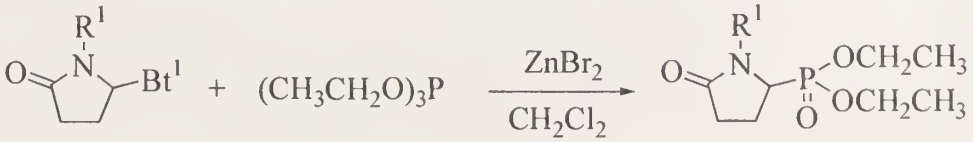
i. Organozinc reagents to give 1,5-disubstituted pyrrolidin-2-ones **6.5** in good yields (Figure 6.3).



6.3 **6.5**

Figure 6.3

A. Triethyl phosphite and zinc bromide to give diethyl 1-(aryl)-5-oxo-2-pyrrolidinylphosphonates (**6.6**) (Figure 6.4).

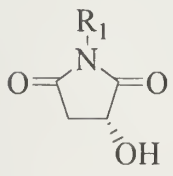


6.3 **6.6**

Figure 6.4

Hydrolysis of these 1,5-disubstituted pyrrolidin-2-ones **6.4**, **6.5** and **6.6** gives γ-amino acids, which are known to be potent inhibitors of the GABA protein. The advantage of this method is that the γ-amino acids can be prepared in two steps. In addition, a variety of substituents can be introduced at the γ position.

Using (S)-malimide (**6.7**) instead of 2,5-dimethoxy-2,5-dihydrofuran (**6.1**) we could synthesize *syn*-β-hydroxy-γ-amino acids, such as (3S, 4S)-statine (**6.8**) [98T12547]. Statin (**6.8**) is a key component of pepstatin, a naturally occurring aspartyl protease inhibitor [98T12547] (Figure 6.5). In addition the corresponding *anti* oriented (3S, 4R) or (3R, 4S)-β-hydroxy-γ-amino acids (**6.9**) could be synthesized. They are present in a variety of anticancerous and antineoplastic natural products. Hapalosin (**6.10**) is a novel cyclic depsipeptide isolated from the cyanobacterium *Hapalosiphon welwitschii*. It exhibits multidrug resistance reversing activity [98T12547].



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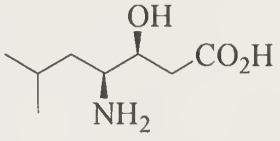

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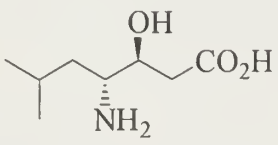

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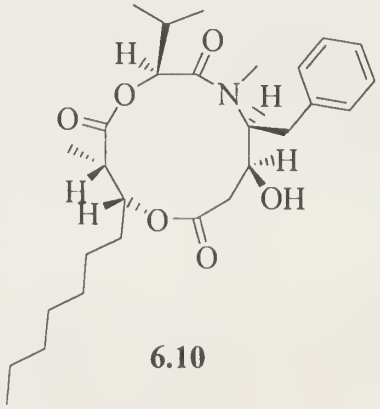


6.10

Figure 6.5

Chapter 3 deals with the syntheses of pyrrolo-isoquinolinones and indolo-isoquinolinones by intramolecular cyclizations of 1-arylethyl-5-benzotriazolyl-pyrrolidin-2-ones and 3-benzotriazolyl-2-arylethyl-1-isoindolinones (Figure 6.6). Thus 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones (**6.11**) and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones (**6.12**) were prepared by intramolecular cyclizations of 1-arylethyl-5-benzotriazolylpyrrolidin-2-ones (**6.13**) and 3-benzotriazolyl-2-arylethyl-1-isoindolinones (**6.14**) respectively, in the presence of titanium chloride. High stereoselectivity was observed in products prepared from chiral amines.

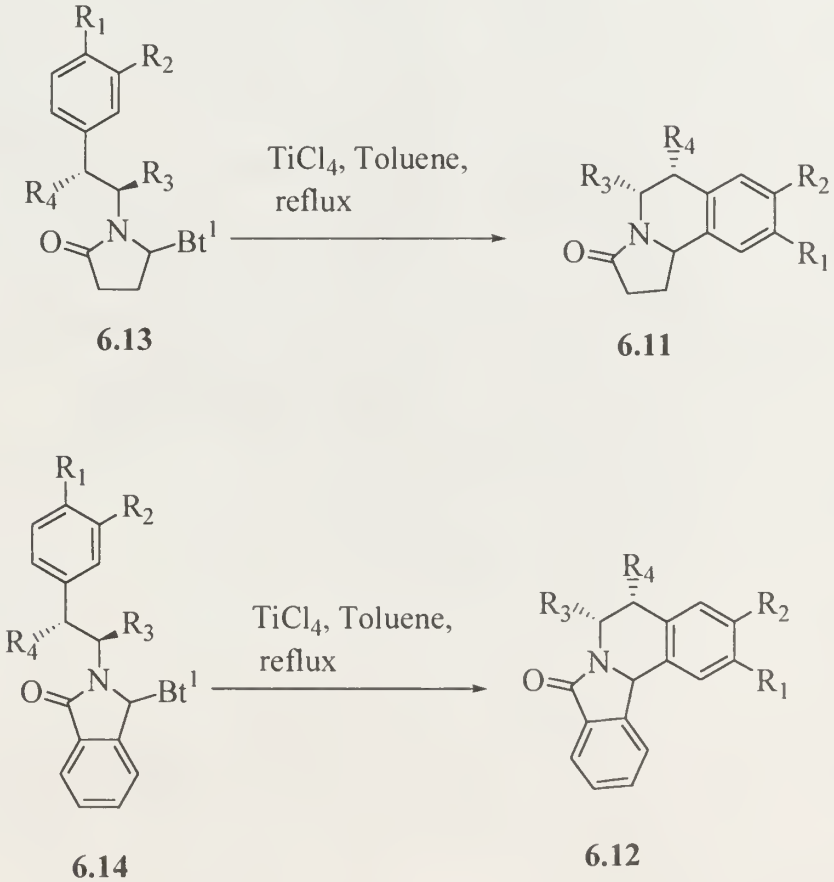


Figure 6.6

Thus we prepared chiral 1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-ones (**6.11**) and 5,12b-dihydroisoindolo[1,2-*a*]isoquinolin-8(6*H*)-ones (**6.12**) in a small number of steps from readily available starting materials in good to excellent yields. The other advantage of this method is that it has four points of diversity and hence a variety of groups can be attached at different positions.

In Chapter 4 the synthesis of chiral benzodiazepines **6.15**, benzoxapines **6.16** and

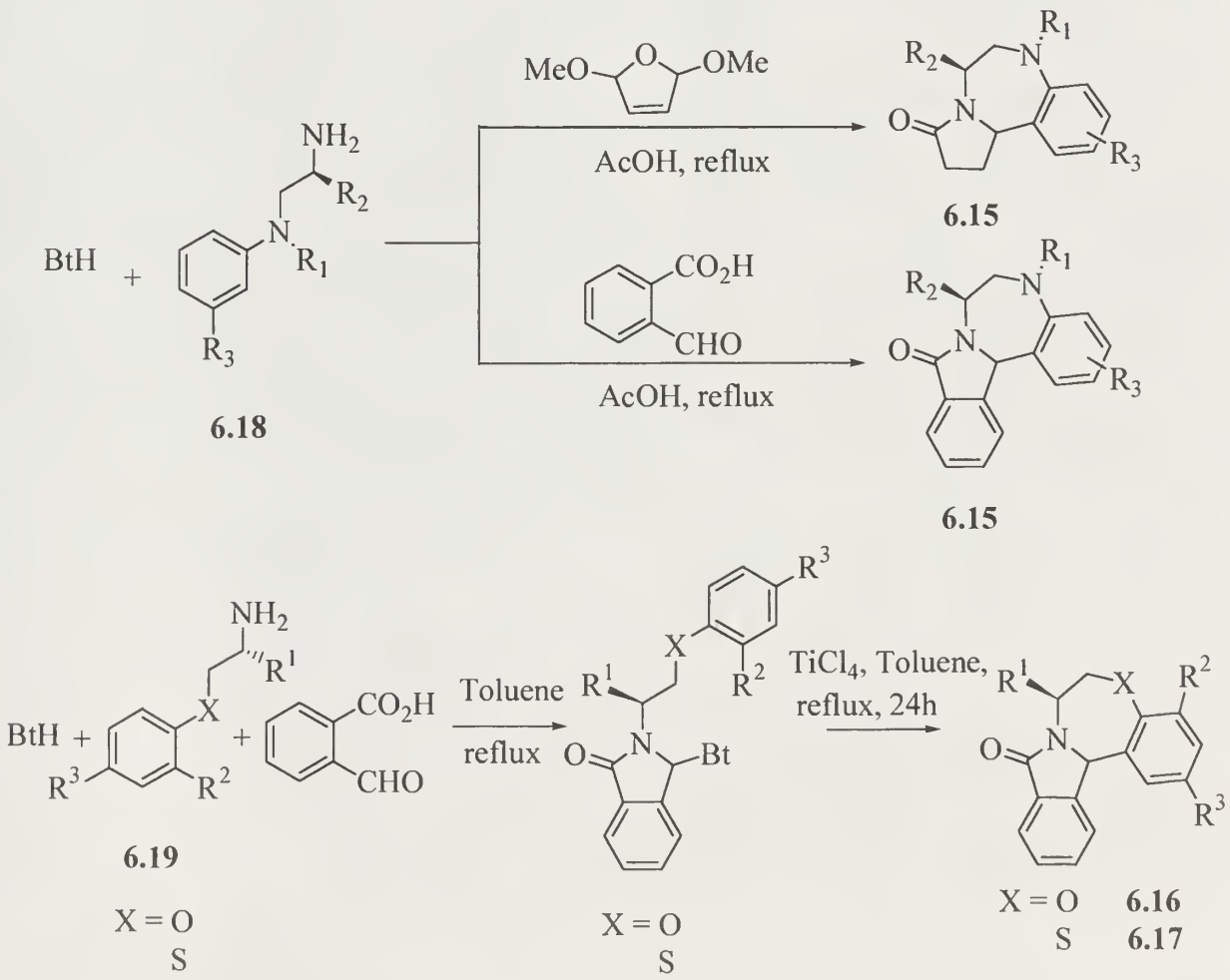


Figure 6.7

benzthiazopines **6.17** is discussed. Lewis acid mediated cyclizations of easily prepared starting materials **6.18** and **6.19** produced novel benzodiazepines **6.15**, benzoxazepines **6.16** and benzothiazepines **6.17** in high yields (Figure 6.7).

Thus, our above methodology of synthesizing chiral benzodiazepines **6.15**, benzoxazepines **6.16** and benzothiazepines **6.17,** utilizing readily prepared starting materials, has the following advantages:

A. Has four points of diversity and hence a variety of groups can be attached at different positions on the basic framework of the molecule.

B. Could be easily amenable to solid phase or combinatorial synthesis.

C. Products are easy to purify and isolate and

D. Since only a few steps are involved, large-scale synthesis is possible.

Finally, Chapter 5 deals with the synthesis of heteroaryl benzotriazole compounds, *N*-substituted-2-(benzotriazol-1-yl)isoindoles **6.20**, pyrroles **6.21**, and 2-(benzotriazol-1-yl)furan (**6.22**). Efficient one step syntheses of *N*-substituted-2-(benzotriazol-1-yl) isoindoles **6.20** and pyrroles **6.21** were affected by reactions of primary amines **6.2** with *o*-phthalaldehyde (**6.23**) and 2,5-dimethoxy-2,5-dihydrofuran (**6.1**) respectively in the presence of benzotriazole. Reaction of 2,5-dimethoxy-2,5-dihydrofuran with benzotriazole gave 2-(benzotriazol-1-yl)furan (**6.22**) (Figure 6.8).

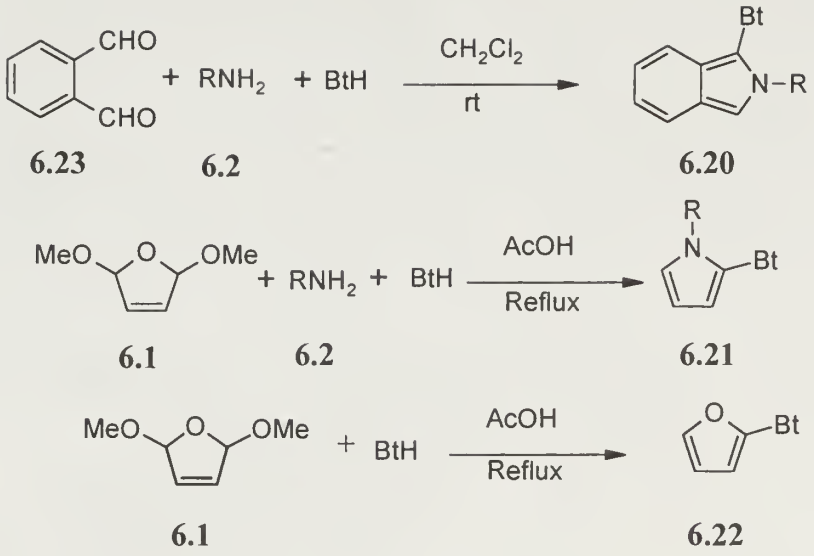


Figure 6.8

These are novel hetero-aromatic compounds having the benzotriazole moiety. Furans and substituted furans have been important molecules in Diels-Alder chemistry [97T14179] for the synthesis of natural products. The benzotriazole at the 2-position of the furan would be critical. After the Diels-Alder reaction, the 2-position, which is a masked aldehydes, could be suitably transformed. Furthermore, the benzotriazole could be easily displaced to put in another substituent.

6.1 Conclusions and Future Work

In an interesting paper, Stuart Schreiber [82TL3867] has shown that ozonolysis of an alkene, such as say cyclohexene (**6.24**), could result in a variety of products, depending on the conditions of the reaction workup (Figure 6.9).

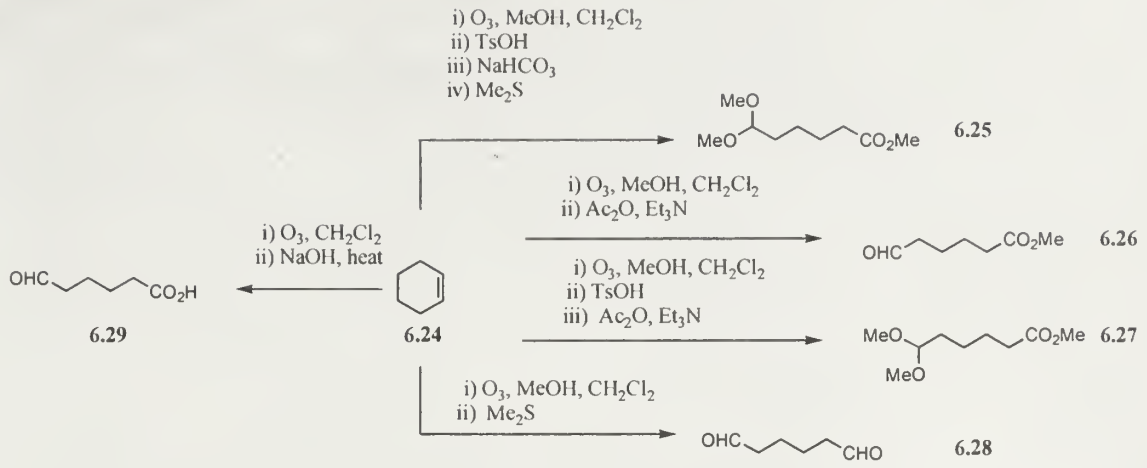
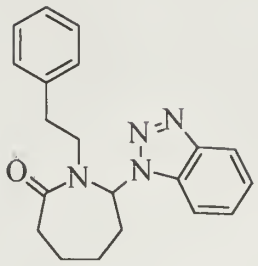


Figure 6.9

To date, such an ozonolysis on a simple chiral alkene such as cyclohexenol or 2-methyl cyclohexene has not been reported. Instead of using cyclohexene, one could use chiral 4, 5, 6 and 7 membered cyclic alkenes. Treating these open chain compounds with benzotriazole and an amine one could make a variety of ring systems after cyclization (similar to Chapters 3 and 4). For example, using a chiral cyclohexene (six carbon atoms) and producing intermediate **6.26** or **6.29** one could synthesize the seven membered ring intermediate **6.30**. This compound could then in turn be used to synthesize a variety of ring systems (viz. 5,7 or 6,7 or 7,7) as shown in Figure 6.10.



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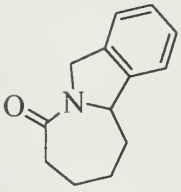

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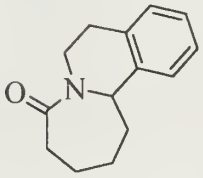

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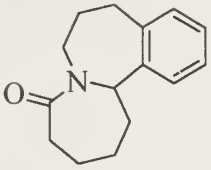

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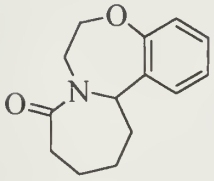

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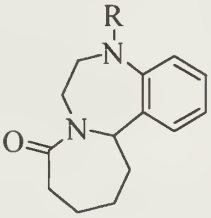

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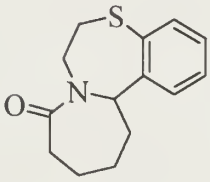
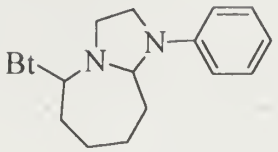


6.36

Figure 6.10

If one obtains the bis-aldehydes **6.28** by ozonolysis, these could be treated with a diamine and benzotriazole to give chiral intermediates **6.37** or **6.38**. These could then undergo substitution reactions to displace both the benzotriazole (Chapter 2) and the pendant heteroatom in **6.37** (NPh) or **6.38** (O). Finally, removal of the aromatic group on nitrogen by hydrogenation would give us chiral mono substituted or di-substituted azepanes **6.39** (Scheme 6.11).



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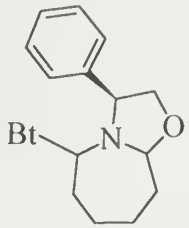

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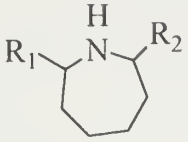

6.39

Figure 6.11

Therefore, we do not have to restrict ourselves to commercially available substrates such as 2,5-dimethoxy-2,5-dihydrofuran (**6.1**) or 2-carboxybenzaldehyde for the synthesis of heterocycles. Any alkene for that matter could be used as a starting material. In addition, ketones could be converted to their enol ethers and also be ozonolyzed to give you the same products.

Thus by using benzotriazole one could make a variety of new ring systems that could be both synthetically challenging as well as biologically interesting.

As stated before, for the past decade and half, the Katritzky group has been actively researching and developing new methodologies for benzotriazole application in chemical syntheses. The work of this thesis is an effort to further our understanding of benzotriazole chemistry and increase its utility in organic synthesis. We have been able to synthesize new molecules containing benzotriazole. In addition, we have been able to transform them into novel and useful heterocyclic compounds in a few numbers of steps.

REFERENCES

The reference citation system employed throughout this dissertation is the one described in "Comprehensive Heterocyclic Chemistry II", Pergamon Press, 1996 (Eds. A. R. Katritzky; C. W. Rees and E. Scriven.).

In the dissertation, a reference is cited by a "number and letter code" appearing in brackets, e.g. [00ABC000]. In this code, the first two digits denote the year of the twentieth century, the letter code represents the name of the journal or book cited and the last digits represent the starting page number in the journal or book in question. In addition, the following convention applies:

A. the year 2000 is represented by 000

B. for journals not commonly cited the letter code is MI and

C. journals which are published in more than one part (or volume) per year, have the appropriate part (or volume) number included in the abbreviated code e.g. [85JCS(P1)2725].

The references are catalogued below by listing them serially based on the year code. Wherever the year code is the same, the listing is alphabetical based on the journal code. And finally, in those cases where the year and the journal codes are identical, listing is based on the page number code. Each reference code is followed by the conventional literature citation in the format advocated by the Journal of Organic Chemistry.

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BIOGRAPHICAL SKETCH

Shamal Mehta was born on June 28, 1970, at Bombay, India. He grew up in Bombay and received his secondary education at the Cathedral and John Connon High School. He attended Jai Hind College for two years and was admitted to the Indian Institute of Technology, Bombay, in 1989. He obtained his 5-year Intergrated M.Sc. in chemistry from the IIT and was awarded the Institute silver medal. He enrolled at Columbia University, New York, from where he obtained his M.Phil. degree under the guidance of Professors Gilbert Stork and James Leighton. He obtained his Ph.D. degree from the University of Florida in December 2000 under the guidance of the Kenan Professor of Chemistry, Dr. Alan R. Katritzky.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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